

Selected Lectures of the XXII National Congress of the Italian Society of Neonatology (*Società Italiana di Neonatologia, SIN*)

NAPLES (ITALY) • OCTOBER 12TH-15TH, 2016

Guest Editor: Mauro Stronati



HOW TO CITE

[Lecture's authors]. [Lecture's title]. In: Selected Lectures of the XXII National Congress of the Italian Society of Neonatology (*Società Italiana di Neonatologia*, SIN); Naples (Italy); October 12-15, 2016. *J Pediatr Neonat Individual Med.* 2016;5(2):e050248. doi: 10.7363/050248.

LECT 1

LUNG RECRUITMENT STRATEGIES AND EARLY SURFACTANT IN NEONATAL INTENSIVE CARE UNIT. PRESENTATION OF A RANDOMIZED CONTROLLED TRIAL: EFFICACY OF A NEW TECHNIQUE (IN-REC-SUR-E) IN PRETERM NEONATES WITH RESPIRATORY DISTRESS SYNDROME

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The aim of this study (ClinicalTrials.gov identifier: NCT02482766) is to compare the application of a recruitment manoeuvre using the high frequency oscillatory ventilation (HFOV) modality just before the surfactant administration followed by rapid extubation (INtubate-RECRUIT-SURfactant-Extubate: IN-REC-SUR-E) with INSURE alone in spontaneously breathing preterm infants requiring nasal continuous positive airway pressure (CPAP)

as initial respiratory support and reaching pre-defined CPAP failure criteria during the first 24 hours of life: $\text{FiO}_2 \geq 0.30$ on nCPAP (6-7 cm H_2O) to maintain SpO_2 87-94% for at least 30 minutes unless rapid clinical deterioration occurred, respiratory acidosis defined as $\text{pCO}_2 > 65$ mmHg (8.5 kPa) and $\text{pH} < 7.20$ on arterial or capillary blood gas sample, apnoea defined as > 4 episodes of apnoea per hour or > 2 episodes of apnoea per hour when ventilation with bag and mask will be required. In this unblinded multicenter randomized trial, 206 spontaneously breathing infants born at 24⁺⁰-27⁺⁶ weeks' gestation and failing nCPAP during the first 24 hours of life will be randomized to receive an HFOV recruitment maneuver (INRECSURE) or no recruitment maneuver (INSURE) just prior to surfactant administration followed by prompt extubation. Thirty-seven Italian centers are actively recruiting for the trial, which started in November 2015. The primary outcome is the need for mechanical ventilation within the first 3 days of life. Infants in both groups will be considered to have reached the primary outcome when are not extubated within 30 minutes after surfactant administration or when they meet the nCPAP failure criteria after extubation. Until now 76 patients have been enrolled and an interim analysis will be planned when 50 infants will be enrolled in each arm. The analysis will intend to compare treatment arms with respect to efficacy, safety, futility, assessment of difficulties with patient enrolment, and, if necessary, a sample size adjustment. A recruitment maneuver just before surfactant administration has the potential of improving the efficacy of surfactant in terms of a more homogeneous lung distribution and consequent achievement of an optimal functional residual capacity (FRC), as demonstrated in the animal model of RDS. In the era of non-invasive ventilation (NIV) and early rescue surfactant administration with the INSURE approach, a large proportion of extremely low gestational age newborns (ELGAN), on the basis of the current literature data, also fail to reach an optimal FRC and needs subsequent intubation and mechanical ventilation. For this reason the rationale of our study is to realize optimal lung volume recruitment strategy in HFOV just before surfactant administration, followed by prompt extubation. This approach will be compared with the standard practice (i.e. INSURE) in a cohort of 24-27 weeks gestational age infants. The design of the trial will allow us to evaluate not only the primary outcome of the study, i.e. the need of mechanical ventilation

during the first 72 hours of life, but also a series of important issues in the respiratory management of ELGAN:

1. The caregiver's ability to provide a gentle approach from the first minutes after birth, using a more conservative strategy (nasal CPAP) compared to elective intubation at very low gestational ages (24-27 weeks): considering that one of the eligibility criteria is the ability of the newborn to well adapt to the extrauterine life without need of intubation (the babies intubated in the delivery room will be excluded from the study), it will be important to evaluate if during the study period a larger percentage of 24-27 weeks newborns will be managed with NIV in the delivery room, compared to the babies of same gestational age born in the period immediately before the starting of the INRECSURE trial (November 2015). In fact, recent meta-analyses and systematic reviews have shown that non-invasive versus invasive respiratory support in preterm infants at birth is associated with a significant reduction of the incidence of the composite outcome death/bronchopulmonary dysplasia in preterm infants with gestational age < 32 weeks (NNT of 25) and in preterm infants with gestational age < 30 weeks (NNT of 35). The recent European RDS guidelines 2016 regarding delivery room stabilization, recommend to stabilize infants spontaneously breathing with CPAP of at least 6 cm H₂O (the same level provided by our protocol in the delivery room) via mask or nasal prongs (A1).
2. The effectiveness of all forms of non-invasive ventilation in the post-extubation management of these very small and vulnerable preterm infants. We are aware that the INRECSURE does not represent a "magic bullet" for the prevention of lung injury. An important role is certainly played by the appropriate use of the different NIV techniques: CPAP, BiPAP, nasal IPPV, nasal sIPPV, nasal HFOV. Although each participating center will use a specific NIV technique just after extubation, a possible different effect of one technique over another will be evaluated at the end of the study.
3. An ancillary study will evaluate not only the hemodynamic consequences (if any) of the HFOV recruitment maneuver, but also the hemodynamic status of each enrolled patient, to identify the hemodynamic parameters that could affect the response to lung recruitment, defined as reported below.

- a. optimal: if the target FiO₂ of 25% is reached at the end of the recruitment maneuver;
- b. sub-optimal: if the target FiO₂ of 25% is not reached at the end of the recruitment maneuver;
- c. negative: if a deterioration of oxygenation is observed during the recruitment maneuver.

At the end of the study, hoping that the results will confirm our hypothesis, i.e. that a recruitment maneuver just before surfactant administration could enhance surfactant efficacy, the next step will be to design a RCT comparing the INRECSURE approach versus the less invasive surfactant administration (LISA) technique.

LECT 2

CONGENITAL DIAPHRAGMATIC HERNIA

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Congenital diaphragmatic hernia (CDH) is a major malformation amongst neonatal pathologies and is characterized by the presence of an orifice in the diaphragm, which during gestation causes the herniation of the intestinal organs into the thoracic cavity. The incidence of CDH is 1/3,000-5,000 live births and for this reason is classified as a rare pathology. Hernias are classified according to the position of the defect in posterolateral or Bochdalek hernias, which represent 70% of CDHs, in anterior or Morgagni's hernias, which represent around 27% of cases, and in the rarer transverse section type, which represents around 2-3% of cases. Posterolateral hernias occur more frequently on the left (85%), followed by hernias occurring on the right (13%) and rarely bilaterally (2%). The pathogenesis of posterolateral hernias is correlated to the failure to close by pleuroperitoneal membranes of one or both pericardio-peritoneal canals. These membranes allow the thoracic and abdominal cavities to remain connected at the back and the abdominal viscera to go into the thorax. The formation of anterior hernias is correlated to the lack of fusion of the section with the thoracic wall for Morgagni hernias and with the lack of development of the section for retrosternal hernias. The dual hit hypothesis foresees two phases of development of the damage. The first, of a genetic or environmental nature, would occur in

an early stage prior to the formation of diaphragm and would provoke the arrest of bilateral pulmonary development. The second damage would follow the mechanic compression of the intestinal viscera due to their passage through the diaphragmatic hiatus and would worsen the ipsilateral hypoplasia to the defect. The alteration of the retinoid signaling pathway, which is known to have an important role in lung development, was considered to explain the first insult of the dual hit hypothesis. Early diagnosis permits the identification of universally known prognostic factors, which have a fundamental role in possible pre-natal therapeutic approach. Pulmonary hypoplasia is one of the major problems in CDHs: pulmonary hypoplasia is measured by the lung-to-head ratio (LHR), which shows with ultrasound technique the rapport between the pulmonary area contralateral to the hernia and the circumference of the cranium. Measurement of LHR has a limit due to its dependence on the gestational age. The value of LHR increases with the increase of the gestational age independent from the real pulmonary size. To compensate for this limit of measurement, LHR is today calculated as the observed value compared to the observed/expected (O/E) LHR, rendering the parameter independent from the gestational age. Until today the O/E LHR is the prognostic parameter best correlated to the survival of the patients affected by CDH. It is important to stress that the O/E LHR does not only give an estimate of pulmonary hypoplasia but is also a predictive factor of survival, independent of gestational age. In patients affected by severe diaphragmatic hernia, the endoscopic approach of the procedure with the endoluminal positioning of the balloon in the trachea (Fetal Endoscopic Tracheal Occlusion – FETO) seems to improve the survival rate: the tracheal occlusion prevents the leak of pulmonary liquid and allows the increase of intrapulmonary pressure and therefore the cellular stretch, promoting cellular proliferation, alveolar development and an

increased growth of the blood vessels. The FETO procedure is performed between 26 and 28 weeks of gestational age and the balloon, positioned in the middle third of trachea, is then removed after 6 weeks with technical fetoscopy. Since 2012 in our Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico we have treated 25 infants (e.g. 27.9 weeks [26.71-29.09]) with severe CDH (O/E LHR 24.9 ± 4) of whom 18 with left CDH, 6 with right CDH and 1 with bilateral hernia. Hepatic herniation was present in 100% of patients. Upon removal of the balloon the population that underwent FETO presented an increase in the rapport O/E LHR ($47.8 \pm 11.2\%$) and a gestational age at the moment of delivery of 34.6 weeks (32.5-36.7) in line with the data reported. **Tab. 1** reports the survival data. The population treated with FETO presents an increased incidence of PPRM and premature delivery, and a significant increase in the survival of infants affected by serious CDH. In particular with the same o/e LHR, early gestational age at diagnosis it is associated with a lower response to FETO procedure in terms of survival.

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Table 1 (LECT 2). Survival data in the population treated with FETO (Fetal Endoscopic Tracheal Occlusion) in Fondazione Ca' Granda IRCCS compared with other two experiences.

	Fondazione IRCCS Ca' Granda FETO n = 25	European FETO Consortium n = 210	Antenatal CDH Registry PRE-FETO
Survival rate	10/25 (40%)	48%	15-25%
Survival rate severe right-sided CDH	2/3 (66%)	38%	< 15%
Survival rate severe left-sided CDH	4/13 (31%)	49%	24%
Survival rate bilateral CDH	0/1		

CDH: congenital diaphragmatic hernia.

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LECT 3

CONGENITAL HEART DISEASE AND NEONATAL COMPLICATIONS

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Nearly eighty years have passed from first pediatric cardiac surgery procedure, when Robert Gross in 1938 successfully ligated a patent ductus arteriosus of a 7-year-old female at the Children's Hospital in Boston, Massachusetts. From that date, remarkable medical and surgical advance, especially with introduction of cardiopulmonary bypass and deep hypothermia circulatory arrest in the early 1970s, have made correction or palliation of nearly all congenital heart disease (CHD) possible. By the 1970-1980s, primary repair cardiac defects in neonates and young infants was becoming reality and nowadays most newborn infants born with complex heart defect undergo surgery within the first week, before they succumb to the consequences of impaired circulation. Continuous improvements has increased survival for these newborns: in the United States by the beginning of the 21st century, contemporary estimates suggested that 85% of patients born with CHD would survive into adult life. This significantly improved reduction in mortality and morbidity over time are not only a result of progress in surgical techniques and interventions, but also of a better critical care and perioperative management, consequences of a true multidisciplinary approach of neonate with CHD due to the complexity and fragility of these patients. As noted in a different report, coexistence of significant extra-cardiac (ECA) congenital anatomic abnormalities, genetic abnormalities, and syndromes are often present in these patients, with reported estimates in the range of 20% to 30%. The presence of ECA may influence therapeutic strategies and have a significant impact on outcomes and may

complicate perioperative management and change prognosis. Likewise gestational age (GA) and birth weight (BW) may affect outcome. Both prematurity and low BW (LBW) are well-established risk factors for poor outcomes. CHD are associated with small for gestational age and preterm infants have more than twice as many cardiovascular anomalies as do infants born at term and 16% of all infants with CHD are preterm. Study of the Society of Thoracic Surgeons Congenital Heart Surgery Database found that outcomes were worse for neonates born at 37 to 38 weeks gestation compared with those born at 39.5 weeks gestation. Several multicenter studies have confirmed a mortality rate between 1.5 and 4 times higher in LBW, very and extremely LBW infants with CHD compared with their counterparts of similar BW without CHD. Newborns with ECA are roughly twice as likely to be born premature and LBW, both factors that increase the risk of early death.

THE CHALLENGE OF EXTRA-CARDIAC COMPLICATIONS

A complication is an event or occurrence that is associated with a disease or a healthcare intervention and may cause, or be associated with, suboptimal outcome.

Gastrointestinal complications

Necrotizing enterocolitis (NEC) is an acute inflammatory disease with a multifactorial pathogenesis. The risk of developing NEC is inversely related to GA at birth but is also substantial among term infants who have an additional risk factor that predisposes them to bowel ischemia such as CHD. Reports show that NEC occurs 10-100 times more frequently in the CHD population than in term infants without CHD. The risk of NEC is significantly increased in the preterm of whom two-fifth had a functionally univentricular physiology. The highest risk patients have anatomy associated with aortic run-off lesions cardiac defect, and the most commonly associated defects are hypoplastic left heart syndrome (HLHS). Contributor to the development of the NEC may be related to intestinal hypoperfusion and/or chronic hypoxemia, and episodic low cardiac output syndrome or shock. NEC can be a particularly devastating complication, and this should stimulate enhanced surveillance for its detection and prevention in neonates with CHD.

Congenital gastrointestinal system malformations

In newborns, congenital gastrointestinal system malformations (GISM) mainly result in symptoms of intestinal obstruction and often require surgical intervention in the early days of life. Intestinal

rotation abnormality (IRA) is an anatomical defect during embryonic development of intestinal rotation and fixation within the abdomen. IRA is the most commonly identified abnormality in infants with CHD and is frequently observed in patients with heterotaxia, as 40% to 90% of these patients have IRA. In its most severe form, malrotation results in a narrow mesenteric pedicle and predisposes to midgut volvulus, thus leading to small bowel ischemia and infarction, an often fatal condition in the neonate. Other GISM are also present and more easily recognizable as anal atresia, esophageal atresia.

Neurological complications

The results of a recent meta-analysis suggest that CHD is associated with an unexpectedly high prevalence of prenatal structural brain abnormalities, reduced brain volume, delay in brain maturation and altered brain circulation. The most commonly reported abnormality was ventriculomegaly. Neuroimaging demonstrates a high incidence of preoperative brain abnormalities ranging from 25-53%, and seems to be greatest in left-sided heart lesions than those in cyanotic defects. However, in a recent study, the type of the CHD was not significantly associated with the risk of abnormal brain development. The major manifestations of neurological injury that cardiac patients face are stroke, hemorrhage, and seizure. Periventricular leukomalacia, the most common ischemic brain injury in premature infants, may be present in up to 50% of all infants with HLHS.

Respiratory complications

VLBW infants with CHD were found more than 4 times as likely to develop bronchopulmonary dysplasia compared with those without CHD, probably due to prolonged mechanical ventilation and pulmonary edema. Phrenic nerve injury resulting in diaphragmatic palsy and paralysis is a cause of respiratory failure in the postoperative period.

Growth and feeding difficulties

Growth failure is a well-described phenomenon in infants with CHD, and the severity of the malformation such as single ventricle physiology leads to worse nutritional status. Factors contributing to malnutrition include decreased caloric intake, increased energy expenditure secondary to cardiac failure and/or increased work. Feeding dysfunction is common in CHD, and it may be related to different impediments as gastroesophageal reflux, dysphagia, oral aversion, laryngopharyngeal dysfunction and vocal cord injury.

Other complications

Although physiologic anemia in healthy term infants is essentially benign, and the threshold for transfusion in preterms remains unclear, it is probably advisable to implement a lower than normal threshold. This is particularly relevant for neonates with functionally univentricular physiology, who are at great risk of tissue hypoxia, and also in the case of simple cardiac malformations such as septal defect with left-right shunt. Infants with HS and Di George syndrome are at high risk of infection as well as preterm infants with CHD. Small studies have demonstrated a greater than 2-times incidence of sepsis in preterm infants with CHD compared with those without infection as well as higher rates of nosocomial infections compared with those born at 39 weeks' gestation.

CONCLUSIONS

Management of infants with CHD poses multiple challenges and requires the collaboration of highly specialized providers from multiple disciplines. Continued collaboration of multidisciplinary teams, including neonatologists, cardiologists, anesthesiologists, cardiac surgeons, and intensivists will be critical in the management of these neonates.

LECT 4

THE EPIGENETIC ROLE IN NEONATAL GROWTH

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Much of human development is completed in early life, in particular during the first thousand days after conception [1]. Epigenetics could explain the impact of environmental stimuli such as nutrition and lifestyle, at any time in life, on the individual programming through the modulation of gene expression with short- and long-term effects on health [2, 3]. The most sensitive time windows for human development, during which programming of growth and metabolic functions takes place, are the prenatal and early postnatal stages of life. According to the Barker's theory, an impaired function of the fetal-maternal-placental unit might result in adaptive responses determining adverse effects on fetal development [4]. Detrimental changes occurring in the intrauterine environment, induced by exposure to cigarette smoking, maternal stress

and maternal malnutrition status during pregnancy, are critical in programming the fetus for an altered phenotype with increased risk of chronic diseases throughout life [2-11]. Developmental consequences resulting from the intrauterine environment may be partly ascribed to epigenetic mechanisms [5-11]. Interesting findings arise from the investigation of genes involved in fetal and placental growth and development such as the insulin-like growth factor 2 (*IGF2*) gene [6-10]. *IGF2* is one of the most well known imprinted genes epigenetically regulated. Variations in the DNA methylation profile of human H19/*IGF2* locus that can be induced, for example, by caloric or protein restriction, dietary micronutrients and cigarette smoking during pregnancy, lead to different outcomes of fetal and placental development and birth weight [6-10]. Epigenetics-related prenatal features affect directly birth outcomes and therefore neonatal growth [10-13]. Incidentally, infants delivered preterm, SGA, LGA or with intrauterine growth restriction appear to have distinct developmental trajectories [10-13]. In order to assess whether growth in early postnatal life is associated with modifications in gene expression ruled by epigenetic processes, the role of IGF1 and leptin has been investigated. The impact of IGF1 in starting an early postnatal rapid growth is elicited by evidences showing different growth trajectories in both preterm and term newborns, AGA or SGA and different IGF1 serum concentration [11, 13]. Results from a recent study reveal that SGA infants with slow growth during the first fifteen postnatal days have lower cord blood IGF1 levels than infants presenting a normal growth [13]. Although genetics seems to be the major source of individual variability in child growth, it has been speculated that epigenetic processes regulating IGF1 gene expression might contribute, at molecular level, to the difference in IGF1 serum levels. Data obtained from peripheral blood mononuclear cells indicate that the methylation of the P2 promoter of IGF1 gene is highly and negatively associated with serum IGF1 and child height growth [14]. The complex balance of growth process in earlier ages is also a result of leptin related functions [15-17]. Leptin is an adipocyte-derived key regulator of appetite, energy intake and expenditure and body fatness through actions in the hypothalamus and is strongly associated with obesity and insulin resistance [15-17]. The possibility that intrauterine leptin exposure may affect early infancy weight gain programming, is supported by the theory that links perinatal leptin concentrations, birth weight and postnatal growth

[15-17]. A lower cord blood leptin level correlate with a decreased size at birth, but is inversely correlated with increased weight gain in the first six months and a higher BMI at three years of age [16]. According to other studies, higher perinatal leptin is associated with lower adiposity at three years of life, whereas higher leptin at three years is associated with greater weight gain and adiposity at seven years [17]. This kind of early growth patterns supports the existence of a window of leptin sensitivity such that leptin exposure in the early postnatal period prevents obesity but exposure later in life does not [17]. Since leptin levels at birth (in the cord blood) and in early postnatal period could also predict growth rates and childhood obesity, epigenetic influences in gene leptin (*LEP*) expression leading to different leptin concentration have been suggested. Evidences from a recent report demonstrate lower methylation of *LEP* and thus an increased expression and higher concentrations of blood leptin in breastfed children at seventeen months of age [18]. The decrease in *LEP* methylation could be one of the mechanisms by which breastfeeding has a beneficial duration-dependent effect on the risk of developing obesity later in life [18]. These findings support the hypothesis whereby leptin concentrations and therefore early growth are programmable by early diet in epigenetic way [18]. Given that epigenetic markers acquired in early life may have consequences later in development, therefore affecting the individual susceptibility to non communicable diseases, intervention strategies, such as an adequate pregnancy monitoring and breastfeeding promotion, should be reinforced, in order to prevent an impaired intrauterine development and a rapid catch-up fat accumulation during early infancy.

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LECT 5

GENETIC BASES OF NEONATAL INFECTIONS

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Neonatal infections are the leading cause of neonatal mortality, with 1.6 million neonatal deaths due to infection estimated to occur annually worldwide [1]. The majority of newborn infants exposed to microorganisms are only colonized and do not develop clinical signs of infection. Conversely, overt infection only occurs in a small proportion of the exposed infants. Currently available preventive strategies rely on epidemiological risk factors, which allow the stratification of infants in groups at high- and low-risk (an estimate of the individual risk) but are unable to accurately predict the risk of developing severe, life-threatening infection at the individual level. Moreover, many cases of neonatal infection occur despite the absence of known risk factors and are currently unpredictable. The understanding of the molecular mechanisms underlying susceptibility to neonatal infection is a key step in the development of more effective and patient-tailored preventive protocols. From a clinical standpoint, we categorize newborn infants suffering from life-threatening infections in two main groups: 1) newborn infants with previous underlying medical conditions and 2) otherwise healthy, full-term newborn infants with no identifiable medical conditions.

NEWBORN INFANTS WITH PREVIOUS UNDERLYING MEDICAL CONDITIONS

These include preterm infants, infants admitted to the neonatal intensive care unit for any reason (exposed to nosocomial pathogens), infants undergoing surgery, infants with any organ disease (including malformations, e.g. urinary tract malformations), and infants exposed to medical procedures or treatments that may *per se* explain an increased risk of infection. Infection in this group is likely to be multifactorial, is facilitated or initiated by the specific medical condition, and is modulated by a number of co-factors including the exposure to antibiotics, the intensive care environment, and the resulting changes in the individual microbiome. Only a small proportion of the individual risk of infection will be explained by individual genetic variations. A reasonable approach to investigate these groups is the design of multi-center genome-wide association studies to assess the association between common or rare polymorphisms and the susceptibility to infection. Such studies may provide some insight into the pathogenesis of infection and unravel the

pathways that are involved in the protective immune response to specific microorganisms [2].

OTHERWISE HEALTHY, FULL-TERM NEWBORN INFANTS WITH NO IDENTIFIABLE MEDICAL CONDITIONS

The observation that monogenic disorders may underlie specific primary immunodeficiency (PID) phenotypes characterized by single-episode and single-microorganism life-threatening pediatric infectious diseases suggests that some neonatal infections occurring in otherwise healthy, full-term newborn infants without any apparent facilitating factor may be, in some cases, the phenotypic manifestation of an inborn error of immunity [3]. Infection in these infants may develop in the presence or in the absence of established epidemiological risk factors, which include increased exposure to the microorganism (e.g. maternal vaginal colonization or maternal mastitis) or conditions known to be associated with the disease (e.g. prolonged rupture of membranes, an older sibling with infection, and others). The latter associate with, but have never been demonstrated to be causative of infection, and may behave as surrogate markers of additional, currently unknown, determinants of susceptibility. Therefore, regardless of the presence of known risk factors, a life-threatening infection that develops in an otherwise healthy, full-term newborn infant must be considered an idiopathic condition. According to the hypothetical, general model of the genetic architecture of human infectious diseases [4], a proportion of these cases may prove to be genetic, due to fully penetrant or incompletely penetrant single-gene defects. In this second group of newborn infants, we further identify three subgroups:

- i. neonatal infections revealing known, classical PIDs (e.g., congenital neutropenia), reviewed in [5];
- ii. newborn – and infant – specific infectious phenotypes, which we define as isolated infections typically occurring during pregnancy or early in life (before the first year of age, often during the first months of life and only rarely affecting other age groups), that may represent the phenotypic expression of novel PIDs. We identify here at least four phenotypes that deserve the design of specific studies:
 - primary respiratory infections caused by RNA viruses. Loss-of-function mutations in *IFIH1*, a cytosolic sensor of the viral RNA, have been implicated as causative factors in some cases [6];

- neonatal group B streptococcal (GBS) disease and listeriosis. These two conditions are uniquely enigmatic and resemble each other in the fact that both typically and specifically affect pregnant or post-partum women and newborn infants. Besides pregnancy and neonates, GBS infection and listeriosis are very rare in the general population and usually cause disease in older adults and/or individuals with underlying medical conditions or with weakened immune system;
 - fulminant, infection-associated, necrotizing enterocolitis in infants with no identifiable facilitating iatrogenic factor or medical condition.
- iii. single-episode and single-microorganism life-threatening infections caused by common pathogens (e.g. *Klebsiella spp.*, *S. pneumoniae*, *S. aureus*) that are non-specific for pregnancy and the neonatal age. Some of these infections, when occurring in older children, have been associated with PIDs (e.g., IRAK-4, MYD88 deficiency for invasive pneumococcal disease, and IL12RB1 deficiency for klebsiellosis) [7-9] but in most cases remain idiopathic. All these cases may benefit from genetic studies targeted to variants in genes defective in known PIDs, or from a next-generation sequencing approach for the discovery of novel, single-gene inborn errors of immunity. We propose a model in which, in the absence of any apparent, non-genetic causative factor, the likelihood of a monogenic condition underlying infection is highest for full-term newborn infants. With decreasing gestational age, the likelihood of a monogenic condition decreases with concurrent increase in co-factors that may partially explain the susceptibility to infection. It is likely that, among newborn infants with life-threatening infection, monogenic conditions of susceptibility will prove to be exceedingly rare, given the strong selective pressure from the environment on genetic variants causing susceptibility to ubiquitous pathogens early in life. However, genetic studies will help to identify the pathways that are non-redundant for the protective innate immune responses to neonatal pathogens and develop novel hypotheses to explain non-genetic infections. The generation of a comprehensive model to understand the susceptibility to neonatal infection is required for the development of effective strategies aiming at accurately

preventing infection in high-risk individuals rather than in high-risk groups.

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LECT 6

MALFORMATIVE SYNDROMES IN NICU: MANAGEMENT AND GENETIC COUNSELING

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Dysmorphology implies the study of human congenital defects and abnormalities of body structure. Congenital anomalies, present in about 3% of all newborns and in at least 10% of all NICU admissions, are responsible for a large proportion of

neonatal and infant morbidity and deaths. An accurate diagnosis allows prognostic evaluation, specific and adequate follow-up, informed management decisions, assessment of recurrence risk and prenatal diagnosis in future pregnancies. Neonatologists are often the first physicians to evaluate newborns affected with congenital defects and consequently they are central figures to identify patients requiring further screening for occult malformations, and to perform diagnostic testing. A newborn with congenital anomalies can be an unexpected event at birth, though there have been major advances in prenatal diagnosis with increasing detection rates of fetal structural anomalies at earlier gestations. As there are thousands of rare malformation syndromes, it is not possible to memorize each syndrome. A systematic approach is essential and includes the knowledge of classification and etiologies of anomalies, a family and perinatal history, a clinical exam, a targeted imaging study, laboratory and genetic tests and the use of databases. In general, “anomaly” indicates a structural abnormality of any type, excluding anatomical variations, and it is classified in four clinically significant types: malformation, disruption, deformation, and dysplasia. “Malformation” is a morphologic abnormality of an organ, part of an organ, or larger region, that arises because of an intrinsically abnormal developmental process. “Disruption” indicates a morphological defect due to the extrinsic breakdown of, or an interference with, the originally normal developmental process. They usually include alterations following exposures to teratogens, such as drugs and viruses, or vascular (e.g., in fetus with homozygous α -thalassemia) or mechanical events (i.e. amniotic bands). “Deformation” is an abnormal shape, form, or position of a part of a body that results from extrinsic or fetal mechanical forces that distort otherwise normal structures. Examples of deformations include tibial bowing, micrognathia, and some forms of arthrogyposis. “Dysplasia”, abnormal cellular organization into a tissue resulting in structural changes, often affects several organs, such as cartilage and bone in skeletal dysplasias, skin and brain in neurocutaneous disorders, or skin, tooth, hair, and nail in ectodermal diseases. Groupings of congenital anomalies are divided into syndromes, associations, sequences, and complexes, based on the frequency with which the features are seen together and whether a known etiology exists. A “syndrome” is a pattern of multiple anomalies that occur in a consistent pattern and with a common genetic etiology. “Associations” consist of non-

random occurrence in two or more individuals of multiple anomalies not known to be a syndrome or a sequence, that do not have a predictable pattern. An association could become a syndrome if a common etiological cause is identified, like the case of CHARGE syndrome. A “sequence”, a pathogenetic and not a causal concept, results from a cascade of developmental consequences that proceed from a single defect. Examples are Pierre Robin sequence, early urethral obstruction sequence, and Potter sequence. The causes of congenital anomalies are often divided into genetic factors, including structural and numerical chromosome abnormalities, monogenic mendelian diseases, imprinting defects, dynamic mutations, and environmental factors. Many common congenital anomalies (e.g., cleft lip, cardiac defects, pyloric stenosis, clubfoot) recognize a multifactorial inheritance, for which a familial clustering is observed. A good history should include a detailed three generation pedigree analysis, parental ages at the time of conception, parental consanguinity, history of stillbirths and exposure to teratogens, maternal disorders and infections, and the presence of fetal macrosomia and/or growth restriction. A clinical diagnosis of a pattern of malformations cannot be made on the basis of a single defect, but it usually depends on the recognition of the overall pattern of anomalies, and the detection of minor defects may be as helpful as the detection of major ones. A “major anomaly” is one that has severe medical or cosmetic consequences, including mental retardation and growth failure. A “minor anomaly” represents a medically insignificant departure from normal development occurring with variable frequencies in the normal population, though they alert clinicians of possible coexistence of major anomalies. The likelihood of having a major anomaly, which may be occult, increases with the number of minor anomalies present. In the case of a newborn baby carrying two major anomalies, or one major and two minor anomalies, or three minor anomalies, the neonatologist has to look for occult associated anomalies. Ultrasound exam can be considered a first level imaging investigation. “Brain ultrasonography” is the first choice test in search of possible brain malformations. “Spinal ultrasound” is generally carried out in the presence of abnormalities of the skin overlying lumbosacral region, potential markers of an occult spinal dysraphism, as larger defects may be detected prenatally or are obvious at birth. “Echocardiography” is needed for several reasons: significant proportions of cardiac mal-

formations are associated with extracardiac malformations and/or occur as components of a genetic syndrome, specific cardiac malformations recur more frequently in specific syndromes guiding the diagnosis, associated with prognostic and therapeutic information. Skeletal radiographic exam is mandatory in newborns with segmental defects or with skeletal disorders with disproportion. Approaching a newborn with multiple defects, physicians should keep in mind that: different phenotypes can be shown by patients with identical mutations as underlying incomplete penetrance or variable expressivity; the same morphological defects can occur as an isolated abnormality in an otherwise normal individual, be part of a chromosomal disorder, constitute a feature of a monogenic syndromes or be the consequence of *in utero* exposure to drugs; different phenotypes could have the same etiology; not all cardinal features are presents at birth. The clinical diagnosis could be a fast recall of the facial *Gestalt*, but it is not usually reached only by putting together all the abnormal findings. It is the result of a process which may include prioritizing of the importance of a feature upon its rarity of occurrence, consultation with colleagues and clinical geneticists, and the use of textbooks, or of databases.

LECT 7

NEWBORNS OF MOTHERS WITH AUTOIMMUNE DISEASE

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The possible effects of maternal autoimmune disease (AD) and associated treatment on the fetus and newborn infant have been studied during recent years. Neonatal lupus erythematosus (NLE) is a model of passively acquired AD due to placental transfer of maternal anti-SSA/Ro and anti-SSB/La antibodies. The most serious clinical manifestation of NLE is the autoimmune-associated congenital heart block (CHB), which typically develops *in utero* during the second or third trimester of gestation [1]. Complete CHB seems to be irreversible and carries a significant morbidity and mortality risk.

The frequency of third-degree block in an offspring of a mother who has anti-SSA/Ro antibodies is estimated at 1-2%. Non-cardiac manifestations of NLE include the usually photosensitive cutaneous rash that presents with erythematous skin lesions, hepatobiliary disease and hematologic abnormalities [1, 2]. These less frequent manifestations of NLE are generally transient with spontaneous resolution. Antiphospholipid syndrome (APS) is an autoimmune-mediated clotting disorder characterized by thrombosis and morbidity during pregnancy in association with antiphospholipid antibodies (aPL) [3, 4]. Pregnancy complications, including early and late pregnancy losses, pre-eclampsia and pre-term delivery, are frequent in women with aPL [5, 6]. A European, multi-centre, prospective study which followed a cohort of children born to mothers with APS has shown that, apart from prematurity (16% of neonates) and the related complications, neonates had no other clinical manifestations of APS [7]. In particular, no cases of neonatal thrombosis have been reported, suggesting that placental transfer of aPL is not necessarily associated with aPL-related clinical manifestations in newborns. Cerebral ultrasound abnormalities, including subependymal pseudocysts, increased echogenic white matter and sonographic lenticulostriate vasculopathy, have been documented in neonates from mothers with AD [8, 9]. However, no perinatal factors as pre-term delivery, low birth weight, maternal drug treatment or placental transfer of auto-antibodies resulted independently associated to this finding, suggesting a multi-factorial pathogenic mechanism in foetal neurologic involvement [10]. Taking into account the adverse cognitive function reported in children born to mothers with systemic lupus erythematosus and/or APS, a long-term follow-up could be recommended [11-13]. Finally, studies on the potential effects of immunosuppressive drugs used during pregnancy for AD have showed a normal immune-function in exposed children [14-16].

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LECT 8

PROTECTED DISCHARGE FOR HEALTHY AND SICK NEWBORNS. SWEET HOME, GOOD CARE

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The main scope of the quality of pediatric care is to warrant an integrated approach to the mother-infant dyad after parturition. Such an integrated approach is defined Protected Discharge. Indeed, the post-partum period is a critical clinical challenge for the mother (exposed to risks of post-partum blues or depression, and fatigue), the newborn (weight loss, dehydration, jaundice, and even congenital malformations), and the whole family (impaired family relationships). To avoid or early recognize such problems, it is mandatory to monitor the mother-infant dyad at home within a few days after hospital discharge. A two-way approach should be promoted by the Local Health District. The first one should involve healthy newborns. In such infants, the main scope of the Protected Discharge should be focused on improving the parental-baby relationship, promoting breastfeeding, reducing the incidence of Sudden Infant Death Syndrome, implementing vaccination culture, preventing domestic accidents, and supporting all families which are in disadvantaged social-economic conditions (nearly 25% of total population). The second one is focused on sick newborns which, at home, need medical care, nurse assistance, and/or rehabilitative programs because of brain, nerve, or muscle damage. This integrated approach should replicate, both in quality and frequency, programs potentially implementable in hospital settings. Protected Discharge should be provided for both healthy and sick newborns. In Italy, the proportion of newborns for which Protected Discharge should be provided is nearly 550,000 infants/year. Twenty-five percent of such infants are premature, and 0.9% of them show a birth weight lower than 1,500 g. Main characteristics of an effective Protected Discharge are a strict cooperation between hospital and community physicians and the active participation of parents. Moreover, at home, both pertinence and appropriateness must characterize any intervention focused on promoting the mother-infant dyad well-being, attenuating social and relational risk factors, and implementing all factors protective which are protective toward the infant and the mother health. Pertinence/appropriateness are the main factors of

any Protected Discharge, which should be planned in accordance with the inputs established by hospital and community physicians and the special care needs of the mother-infant dyad. All such conditions identify a correct Birth Path planned (through an effective cooperation between hospital and community health services) in accordance with the guidelines of Quality Management of pregnancy, delivery, and puerperium and the quality of assistance provided by different community health services.

DISCHARGE CRITERIA

Healthy newborns

For such infants, discharge should happen within 48-72 hours after birth, but only in the presence of a normal clinical course, clinical examination not showing suspicion of diseases requiring further hospital monitoring, identification of local community health services which are able to satisfy any need care of the baby and its family, and a prompt and informed community care of the newborn by the family pediatrician through a strict and effective cooperation between hospital and community health services. The choice of the family pediatrician should happen before hospital discharge. In this way, the exchange of clinical information between hospital and community clinicians is facilitated. Another way to facilitate an effective cooperation between hospital and community health services is to establish e-Health services (including health electronic card and electronic medical records).

Sick newborns

For such newborns, suffering from transient or enduring illnesses, it is mandatory for the hospital care team to establish a program labeled Therapeutic Care Plan (which assesses point-by-point the community health assistance) preparatory to the launch of the Integrated Therapeutic Assistance (which includes interventions by pediatricians and other clinicians useful in managing specific clinical conditions, Psychologists, Social Workers, Nurses, and Physiotherapists) and the Integrated Care Plan (a tailored plan including several social and health supports performed in co-management with Specialized Health Centers).

Newborns of immigrant mothers

For such newborns of mothers coming from high migratory pressure countries, cultural mediation and information about the availability of local health and social services and their managers professionals must be provided. About 400 infants/year are born to immigrant or teen-ager mothers and are abandoned.

CONCLUSIONS

For such reasons, Birth Plan and Protected Discharge both are specific opportunities to improve hospitality culture, competence in identifying all special needs of care of the mother-infant dyad among all professional operators involved in such programs, and to warrant effective responses to new and emerging social and health needs of the mother-infant dyad.

LECT 9

THE NEW INTERNATIONAL GROWTH STANDARDS FOR PRETERM INFANTS

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Preterm birth is the most important cause of perinatal mortality worldwide and the second largest cause of death in children below 5 years of age. For the surviving infants, there is an increased risk of developing a range of health problems in later life, such as high blood pressure and impaired neurodevelopment, especially if they were born extremely preterm and/or with low birth weight. Therefore, ensuring that postnatal growth is as healthy as possible is critical to improving survival and long-term outcomes in preterm infants. This implies having reliable charts to assess their growth, which is challenging in preterm infant population given the lack of consensus regarding the most suitable charts to use [1]. The charts that have been proposed for clinical assessment can be classified into the following categories: 1) fetal weight estimation curves based on ultrasound measurements: they may not be reliable because, by definition, estimated fetal weight represents an estimate of actual weight and large measurement errors are known to exist; furthermore, these fetal charts do not take into account the physiological weight loss that occurs in the neonatal period. 2) Birth weight for gestational age charts: data used to construct them are cross-sectional and are not representative of the growth of preterm infants that occurs during extrauterine life. They are in fact constructed using cross-sectionally collected anthropometric measures taken at birth in infants born at different gestational ages. 3) Postnatal longitudinal growth charts for preterm infants: most of the available charts concentrate

on VLBWI (birthweight below 1,500 grams) divided into birthweight intervals, not considering their gestational age, and therefore including fetal growth restricted infants; they seldom have early ultrasound dating or reliable last menstrual period date; usually, infants born to mothers with diseases that could impair fetal growth and lead to newborn complications are included; most of them do not specify feeding practices and have relatively short follow-up periods. 4) Prescriptive growth standards for infants born at term (however, when used to monitor preterm infant growth, their measures often fall far below the lowest centiles or Z scores, as the postnatal growth pattern of preterm babies is not the same as for term infants). 5) A combination of birth weight for gestational age charts with prescriptive growth standards for term babies, e.g. the Fenton growth charts [2]: this combination maintains the same issues listed above for each of its components except that they usually have larger sample sizes for the very preterm gestational ages.

For all these reasons, it is recognized that longitudinal charts specifically built for preterm infants should be used. We therefore performed a systematic review of longitudinal studies, with two or more measurements of a participant over time, in which the primary aim was to build longitudinal growth charts for preterm infants. The overall quality of methods in the included studies ($n = 61$) was acceptable or low on the basis of the a priori quantified criteria. The most common shortcomings detected were unreliable anthropometric assessment, gestational age estimated late in pregnancy or only by last menstrual period, duration of follow-up, reporting of postnatal care and morbidity, assessment and management of outliers, choice of the covariates, and the presentation of charts [3].

To overcome these problems the international INTERGROWTH-21st Project was launched and assessed fetal, newborn, and postnatal growth of preterm infants in eight different countries around the world, in which pregnancy and mother care and nutritional requirements were satisfied. From these populations, the Fetal Growth Longitudinal Study enrolled healthy women who started antenatal care in the first trimester of pregnancy and assessed fetal growth by ultrasound. All preterm infants born to these women were eligible for the Preterm Postnatal Follow-up Study, which included standardized anthropometric measurements, feeding practices based on breastfeeding, and collection of clinical outcomes on morbidity, treatments, and development. This strategy provided a population that

was conceptually similar to the one selected with a prescriptive approach for the creation of the infant and child growth standards of the World Health Organization [4]. To construct the preterm postnatal growth standards, the following exclusion criteria were applied: multiple birth, stillborn, GA < 26 or ≥ 37 weeks, congenital malformations, intrauterine growth restriction, or severe postnatal morbidity. Data were pooled from study sites and stratified by postmenstrual age. For neonates, males and females were studied separately. The new preterm growth standards [5] differed in the pattern from those for babies in the INTERGROWTH-21st Newborn Size Standards [6]. The curves overlap with the WHO Child Growth Standards for term babies [4] by 6 months of corrected age. These new standards represent a valid tool for monitoring postnatal growth in preterm babies, especially for moderate (32-34 weeks of GA) and late preterm (34-36 weeks of GA at birth). The new postnatal growth standards for preterm infants are available as percentiles and as z-scores, in order to allow the clinician to easily assess the pattern of postnatal growth and changes in z-scores over time [7]. This use of these standards is preferable instead of the cross-sectional charts of size at birth to evaluate preterm infants until 6 months of corrected age, after which use of the WHO Child Growth Standards is recommended. When integrated, the INTERGROWTH-21st Newborn Size Standards [6], the Preterm Postnatal Growth Standards [5], and the WHO Child Growth Standards [4] will allow researchers and clinicians to make comparisons and assessments throughout infancy and among populations.

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LECT 10

HOW AND WHEN TO TREAT THE PDA

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Sixty years after prolonged patency of the ductus arteriosus was recognized as a frequent occurrence in preterm infants, the best strategy for treatment remains unknown, and the very necessity for treatment has been called into question. Demonstration that ductal closure can be safely and reliably achieved by surgical ligation and the discovery that nonsteroidal anti-inflammatory drugs induce ductal closure, combined with strong epidemiological associations of PDA with numerous morbidities and higher mortality, led to widespread adoption of those treatments. The expectation that early treatment would reduce adverse outcomes, particularly including death, bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment, has not been realized, however. Meta-analyses of more than 50 randomized controlled trials, which enrolled more than 5,000 preterm infants, demonstrate that despite efficacy in achieving ductal closure, treatment does not result in lower rates of any adverse outcome. The sole exception is reduced intraventricular hemorrhage > grade 2 by indomethacin prophylaxis, which neither depends on PDA closure nor improves long-term neurodevelopment. This lack of demonstrable benefit from medical or surgical PDA closure is not an artifact of open-label crossover to treatment in the control groups of those trials, as meta-analysis results are not different after exclusion of trials in which open-label treatment rates exceeded 50% or were not stated (leaving 28 trials and 3,749 subjects). Restriction to studies reported since 1990 (the post-surfactant era) and for which the mean gestational age of the subjects was ≤ 28 weeks (10 trials, 2,813 subjects) also does not alter the outcome, refuting

concerns that the data may be too old or include too few extremely low gestational age infants to be relevant to current practice. Because most trials (31, including 4,126 subjects) initiated PDA treatment at a mean postnatal age ≤ 5 days, the evidence for lack of benefit from treatment is strong only with respect to early, nonselective treatment strategies. Results of studies for which age at initial treatment was not specified (13 trials, 640 subjects) did not differ from those of early treatment. Only 8 trials, including 250 subjects, initiated treatment at a mean postnatal age ≥ 7 days; these trials were all conducted before 1983 and most did not report outcomes other than ductal closure (increased) and mortality (not changed). Accordingly, the hypothesis that treatment of PDA after the first postnatal week may be beneficial remains untested, and such treatments must be regarded as unproven therapies. Data from randomized trials have failed to confirm early observations of improved pulmonary function after PDA closure; in fact, ligation is associated with prolonged need for mechanical ventilation, indomethacin with increased oxygen requirements and higher mean airway pressures, and ibuprofen with a greater likelihood of requiring more than 30% oxygen at 36 weeks postmenstrual age. In the absence of randomized trials to guide later treatment strategies, observational data can be used to analyze differences in treatments within a cohort or to compare outcomes for cohorts collected during epochs in which different treatment approaches were utilized. The pitfalls of confounding by indication and survivor bias in these analyses are substantial, but some may be instructive. Changing from an early ligation protocol to a more selective and later ligation approach for infants < 27 weeks gestation with persistent PDA after indomethacin prophylaxis and a course of indomethacin treatment reduced the rate of ligation in this high-risk group from 100 to 72% and increased the median age at PDA closure from 14 to 23 days and the median duration of exposure to ductal shunting from 2 to 17 days. Although longer exposure to PDA might be expected to lead to worse outcomes, no adverse consequences were evident; the unadjusted odds of death or BPD were significantly lower (0.42, 95% CI 0.18-0.96; not confirmed in adjusted models), as were the adjusted odds ratios for both NEC and abnormal neurodevelopment. Ligation at < 10 days of age was associated with a much higher rate of abnormal neurodevelopment (OR 11.4, 95% CI 1.9-70.7). Deferral of treatment for at least three weeks after birth therefore appears to be at least safe, if not

preferable. Another center reported that delaying ligation until at least 2 weeks was associated with a significantly decreased risk for mortality or morbidity (aOR 0.11, 95% CI 0.012-0.93; adjusted for EGA, birth weight, and oxygen use). The risk of postligation circulatory collapse is lower in infants who have surgery after 28 days of age (6%) than in those who have surgery earlier (28%). The decision to treat should be guided by echocardiographic confirmation of hemodynamic significance (e.g., PDA diameter > 2 mm, holodiastolic reversal of flow in the descending aorta). There is insufficient evidence to guide the choice between medical (indomethacin, ibuprofen, paracetamol) and surgical treatment (ligation). If the ductus must be closed, treatment can be deferred until the third or fourth postnatal week; in particular, ligation appears to be safest if performed after 28 days of age. A number of recent reports have described results of even more stringently noninterventional strategies for PDA management in preterm infants. These reports indicate that spontaneous PDA closure can be anticipated in approximately 90% of infants, and that persistent PDA often does not prevent discharge from the hospital. Adoption of such an approach at one center was followed by a reduction of a very high PDA treatment rate (including ligation in 82%) to zero, with no change in mortality and a reduction in the rate of BPD from 58% to 38%. These observations should provide motivation and equipoise for randomized trials of highly selective strategies for PDA treatment.

LECT 11

HEMODYNAMIC EVALUATION OF INFANTS WITH RESPIRATORY DISTRESS: TIMING AND DIAGNOSTIC PATHWAYS

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Respiratory failure of the newborn is frequently associated with hemodynamic instability. It may be related to an impairment of respiratory function (immature lung, lung infection, meconium aspiration, diaphragmatic hernia) or to cardiovascular compromise (asphyxia at birth, patent ductus arteriosus, congenital heart disease, cerebral vascular malformation). Despite that, very often the progression of the disease involves

both systems and this relies on one of the absolute peculiarity of the newborn: the transitional circulation. Its understanding and the evaluation of intra- and extracardiac shunts is very important for the evolution, the treatment and the prognosis of the disease under study. Invasive but also non-invasive respiratory supports do modify intrathoracic pressure conditions and generate changes in lung volumes. This fact affects the heart chambers and the intrathoracic vessels with an impact on the pulmonary vascular resistances and venous return to the right and left heart. The optimal pharmacological support of inotropic type, vasopressor, vasodilator (nitric oxide, prostaglandins, prostacyclins) cannot be performed without the knowledge of the baseline conditions and the control of the evolution of the heart-lung interactions in a particular clinical scenario. Increasingly in recent years, the pathophysiological reasoning could be supported by some hemodynamic bed-side checks performed by the neonatologist through the development of diagnostic skills traditionally entrusted to cardiologists. In this sense the traditional cardiovascular monitoring (heart rate, blood pressure, urine output, lactate), while remaining of irreplaceable orientation, does not allow the deepening need in terms of estimation of district pressures, flows and vascular resistances. It also gives no information on the status of fetal shunts, the adequacy of venous return and myocardial function. Not helpful, however, in the newborn are the common invasive systems of monitoring released for adult patients. The advent of functional echocardiography, a skill which is possible for the neonatologist who devotes himself to follow a strict and preferably certified training program, has made it possible to unify the resuscitation-ventilation competence with the hemodynamic one, to obtain an integrated, personalized and dynamic care (concept of ongoing evaluation). Since the 2000s the literature has been enriched by many works that have investigated the hemodynamic problems in clinical settings already well known to the neonatologist in respect on the respiratory component. Then, hemodynamic confirmations and surprises have emerged; in particular it has been possible to document very different functional hemodynamic characteristics in patients overlapping for gestational age, weight, severity of lung disease. This hemodynamic heterogeneity may underlie differences in pharmacological response and outcome observed. Despite the large body of literature produced, however, a strong

recommendation about heart and great vessels ultrasound monitoring as standard of neonatal care still lacks. The percentage of neonatologists who can perform an ultrasound examination with a full assessment of hemodynamic function varies in different NICU in different states. In Australia and New Zealand, due to the drafting of the first neonatologist dedicated course, remarkable levels of this empowering have been achieved (> 60%). From a didactic point of view hemodynamic study follows the pathophysiological path rather than the morphological one although competence in the identification of a congenital heart defect is an essential prerequisite for all the neonatologists using the cardiologic probe. Additionally, it should be noted that this assessment may occur in emergency conditions in a severely hypoxic and/or cyanotic newborn and so it must be oriented according to a problem-solving scheme. Examples of this are the echocardiographic evaluation in a term newborn with high oxygen demand: in this clinical setting the estimation of pulmonary pressures, the presence/absence of ductal shunt, the evaluation of the adequacy of the right and left cardiac outputs must be correctly depicted, especially before using nitric oxide. The trap in this scenario for the neonatologist is represented by congenital heart diseases mimicking pulmonary hypertension; the link with a pediatric cardiology service to guide the differential diagnosis is highly wanted. Disputes related to the diagnosis and treatment of patent ductus arteriosus testify to the importance for the clinician to capture a precise hemodynamic diagnostic evaluation to follow the evolution of this often unpredictable anatomical structure in the very low birth weight newborn. It seems reasonable to propose a diagnostic approach that includes early echocardiography (6-12 hours from birth) in all those born < 26/6 weeks of gestational age, instead of reserving a check after 48 h from birth for infants > 27 weeks (hemodynamically significant pre-clinical ductus). A very severe respiratory disease with ventilatory support needing high airway ventilation pressure or requiring recruitment maneuvers will require a careful hemodynamic monitoring oriented to venous return and ventricular performance indices of the right heart; as well as specific conditions such as premature birth from pregnancy complicated by p-PROM (high incidence of abnormal pulmonary vascularization or pulmonary hypoplasia) must be properly framed as a possible indication to use nitric oxide at very low gestational age. Finally do not forget the periodic hemodynamic follow-up,

not easily performed, in the premature infant who has developed bronchopulmonary dysplasia. The application of the latest techniques and sophisticated evaluation of systolic and diastolic performances (tissue Doppler imaging, TDI) is currently being studied for the stratification of cases for long-term therapy using pulmonary vasodilators.

LECT 12

STANDARDS OF CARE AND TECHNICAL STANDARDS FOR THE SAFETY OF THE NEONATAL EMERGENCY TRANSPORT SERVICE (NETS)

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NEONATAL EMERGENCY TRANSPORT SERVICE STANDARDS OF CARE

The aim of the Neonatal Emergency Transport Service (NETS) is to guarantee the best care and stabilization of the neonates at the referral centre, with the most appropriate structural and functional standards, to reduce the additional risk of clinical deterioration during transport [1, 2]. NETS represents the connecting link between birth centers, Neonatal Intensive Care Units (NICUs) and centers providing specialist and surgical care. The Neonatal Transport Index (NTI) (number of neonates transferred per 100 live births) depends on the characteristics of the region covered, including demography, number, level and location of perinatal units. Feasible organizational models, for the optimization of the cost-efficiency ratio, are the following: the “dedicated service”, with an optimal workload of 400-600 transports/year for each Unit; and the “on-call service”, where the transport team can be activated on demand by using personnel temporarily displaced from NICU in areas with a limited workload of 150-200 transports/year [3, 4]. The activation time (time occurring between the intervention request and the team departure) should be less than 30 minutes. A “dedicated” model, staffed by a team of neonatologists supported by experienced neonatal nurses with transport competencies [5], allows to increase quality of NETS with rapid activation times, high operational expertise, fast and

complete epidemiological evaluation and ability to deal with extraordinary situations (transfer of twins, transfers to other regions or abroad). In regional networks where multiple NETS units are present, a NETS coordinating center (CC) should be established. The NETS CC should elaborate diagnostic and care guidelines, control the quality of care provided, monitor the safety and adequacy of transport vehicles and equipment, coordinate the NETS staff training and educational update and plan outreach education programs for the personnel of the referral centers. The NETS CC should adopt an information system for the on-line connection with the NICUs and specialized centers to monitor cot availability, improve the management of the alarm phase and cot research, to ensure optimal care in the most appropriate location for every neonate [6].

TECHNICAL STANDARDS

- *Transport incubator system.* The transport incubator system is a mobile intensive care unit designed to ensure safe microenvironment and suitable protection to the infant [7]. The transparent walls of the hood allow good visual evaluation and access for maneuver is guaranteed by the presence of portholes. A double wall construction ensures optimum microclimate and minimizes heat losses. Forced ventilation ensures a rapid thermal stabilization and maintains an internal positive pressure. A temperature control system limits the possible fluctuations of the temperature set. The infant's comfort is secured by an ergonomic mattress and containment belts. The system is equipped with internal rechargeable batteries for autonomous operation and a power supply for charging. A control panel ensures the management and display of the incubator parameters (air/skin temperature, FiO₂ delivered; SpO₂, heart rate) and of the system alarms. Under optimal conditions the internal CO₂ concentration is ≤ 0.5%. The electro-medical device according to the EU Directive [8] responds to regulatory compliance [9], electromagnetic compatibility and for air-transported patients to the European Aviation Safety Agency regulations [10].
- *Mechanical ventilator.* The mechanical ventilator is ergonomic, compact, impact resistant during transport by ambulance and air, equipped with an anchor system for securing it to the transport incubator system and with a display for rapid and optimal viewing of respiratory settings, parameters and alarms. The ventilator supports modes for invasive (pressure-controlled

and volume-controlled modes) and non-invasive ventilation (including nCPAP) with leaks compensation and synchronization. It conforms to the technical requirements and standards for electromagnetic interference.

- *Humidification system.* Certified humidification system for delivering medical gases in transported infants requiring invasive mechanical ventilation, nCPAP or high-flow nasal cannula (HFNC). Variations of temperature between 30-38°C, relative humidity of 100%, minimum humidity level of 30 mg H₂O/L, maximum flow resistance of 1 cm H₂O at 20 L/min.
- *Multi-parameter monitor.* Shockproof, with intuitive user interface and easy-to-read display for a good visualization of parameters and alarms, graphical display of trends and events, available for wireless telemetry operation. Continuous monitoring during transport parameters: heart and respiratory rates, 3 or more leads ECG, SpO₂, NIBP.
- *Suction unit.* Small, compact and easy portable. Good efficacy and reliability with suction flow between 50-500 mmHg, collecting container with filter and noise level < 70 dB.
- *Modular system for infusion.* Small, impact-resistant, safe and easy to handle. Good performance with flow volume control, programmable infusion rate from 0.01 to 100 ml/h, dose limit, visual and acoustic security alarms for occlusion and free-flow. Protection from defibrillator use, moisture from dripping, compliance electromagnetic immunity, harmonic electromagnetic emissions and flicker [11].
- *iNO.* Reliable electromedical equipment, adaptable and certificated for the use during transport of critical neonates [12]. Gas exposure limits according to directives.
- *Loading stretcher.* Made of light alloy with robustness, safety and optimum maneuverability during transport in the loading and unloading of the incubator transport system

Table 1 (LECT 12). Type-A emergency ambulance: references standards.

EN 3-1	Portable fire extinguishers. Ambulance cab and sanitary cell
EN 737-1	Medical gas pipeline systems – Part 1: Terminal units for compressed medical gases and vacuum
EN 737-3	Medical gas pipeline systems – Part 3: Pipelines for compressed medical gases and vacuum
EN 737-6	Medical gas pipeline systems – Part 6: Dimensions and allocation of probes for terminal units for compressed medical gases and vacuum
EN 738-1	Pressure regulators for use with medical gases – Part 1: Pressure regulators and pressure regulators with flow metering devices
EN 738-3	Pressure regulators for use with medical gases – Part 3: Pressure regulators integrated with cylinder valves
EN 739	Low-pressure hose assemblies for use with medical gases
EN 793	Particular requirements for safety of medical supply units
EN 794-3	Lung ventilators – Part 3: Particular requirements for emergency and transport ventilators
EN 850	Transportable gas cylinders. Pin-index, yoke-type valve outlet connections for medical use
EN 864	Medical electrical equipment. Capnometers for use with humans. Particular requirements
EN 865	Pulse oximeters. Particular requirements
EN 980	Symbols for use in the labeling of medical devices
EN 1041	Information supplied by the manufacturer with medical devices
prEN 1865	Specifications for stretchers and other patient handling equipment used in road ambulances
ISO 5128	Acoustics – Measurement of noise inside motor vehicles
EN 1789	Medical vehicles and their equipment. Road ambulances
EN 60601-1	Medical electrical equipment – Part 1: General requirements for basic safety and essential performance
EN ISO 10079-1	Medical suction equipment – Part 1: Electrically powered suction equipment
EN ISO 10079-2	Medical suction equipment – Part 2: Manually powered suction equipment
PrEN/ISO 15002	Flow-metering devices for connection to terminal units of medical gas pipeline systems
EN 60601-1-2	Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: electromagnetic disturbances – Requirements and tests
IEC 364-7-708	Low-voltage electrical installations – Part 7-708: Requirements for special installations or locations – Caravan parks, camping parks and similar locations
D.L. 553-12/87	Italian law: rules regarding emergency and transport ambulances

with at least two rotating wheels equipped with brake. Load resistance conformity \leq 250 kg, platform for the modules anchorage certificated for the transport and to the safety rules [13].

- **Ambulance.** Designed, built and set up in accordance with EN 1789 and classified as Type A neonatal emergency (**Tab. 1**). Approval after testing of the electrical installation in the sanitary compartment [13]. Testing and validation of the oxygen system and of the medical gas delivery. Sanitary equipment, installed in a workmanlike manner (Italian law 46/90, articles 7-9), have to withstand the 10G test. A stretcher support with hydropneumatic suspension, 10G certified, ensures greater comfort by reducing vibrations and stresses transmitted to the infant during transport [14, 15]. The employer and/or the person in charge must guarantee the equipment periodic maintenance, by specialized technicians, to maintain the safety requirements, and avoid collateral damage to third parties.

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LECT 13

THE CARE OF CRITICALLY ILL INFANTS IN THE NICU: FROM NICU TO PICU

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A growing problem in the management of a Neonatal Intensive Care Unit (NICU) is the request of admission of infants older than one month of life, who are pediatric patients. This phenomenon is due to factors such as the scarcity of Pediatric Intensive Care Unit (PICU) beds, the uneven distribution of the PICUs (of 26 units in Italy, half are in the north and only four in the south), the difficulty of developing a PICU *ex novo* due to the current lack of both economic resources and appropriately trained staff, and the absence of a centralized inter-hospital emergency transport service for critically ill infants. The consequence is that, in some centers, adult intensive care units are often requested to admit pediatric patients. An additional factor that favors the involvement of NICUs in admitting patients beyond neonatal age is the increased survival of infants with a low gestational age (GA). Actually, early preterm birth ($<$ 34 weeks' GA) is associated with some late morbidities such as bronchopulmonary dysplasia (BPD), neurodevelopmental impairment (NDI) and a high risk of hospital readmission in the first years of life. Rates of re-hospitalization in the first year of life increase with decreasing GA at birth, ranging from 13% in infants born at 35 weeks' GA to 31% in infants born at \leq 25 weeks' GA [1]. Moreover, up to 50% of preterm infants with BPD are readmitted to the hospital, frequently to an intensive care unit, during the first or second

year of life [1, 2]. Furthermore, re-hospitalization rates of late preterm infants (34⁰⁷-36⁶⁷ weeks' GA) are two-to-three times greater than those of term infants [3], and the risk of hospitalization is often due to respiratory diseases, such as bronchiolitis [4]. For all these reasons, and even if NICU and PICU would be separate units in an ideal healthcare system, in Italy some hospital managers have decided to entrust the care of critically ill children under the age of one-two years to the NICU team. Infants are actually more similar to term newborns than they are to older children from anatomical and physiological points of view and they have both very similar health issues to those typical at neonatal age and comparable care needs (monitoring, equipment, procedures, indications and dosages of drugs, etc.). Consequently, a NICU team is better qualified to manage the treatment of this particular category of patients. This choice is also based on the simple consideration that, among critically ill patients admitted to a Pediatric Emergency Unit, the percentage of infants and toddlers is usually high. Every year more than 27,000 out-patients are admitted to our department and, among those who need intensive care (red codes, which are nearly 0.6-0.7%), the percentage of children with an age of less than 12 months is about 25%. This percentage increases to approximately 50% if we consider children up to three years of age. Moreover, this strategy allows neonates with chronic or complex disorders, and who thus need a long stay in NICU or repeated hospitalizations, to continue to be cared for in the same unit and by the same staff with many organizational and psychological advantages. This policy was confirmed in a document issued in 2012 by the Italian Ministry of Health [5] which addressed the reorganization of the pediatric network based on different levels of care and which also defined the management of complex acute illnesses and the acute exacerbation of severe chronic disease. This document recognizes the fundamental role of the PICU in the process of reorganization and strengthening of pediatric emergency departments, but also highlights the role of the NICU in the pediatric emergency network as the appropriate structure to address and resolve, in general hospitals where a PICU is absent, the complex acute diseases of early childhood. This strategy has the aims of guaranteeing adequate care to these patients and avoiding admissions to inappropriate departments, such as units where very frequently the continuity in the child's emotional relationships is not ensured during hospitalization.

Intensive care of the critical infant has in any case some peculiarities compared to the intensive care of the newborn and it requires a specific training [6], but certainly the cultural baggage of the neonatal intensivist is a good starting point for expanding his sphere of action to childhood. This activity must obviously be planned in collaboration with the hospital medical management and carried out in dedicated areas, with suitable equipment and according to well defined educational programs. Also the transportation of the critically ill infant is a major health care problem, which has so far been completely ignored. It is equally important that the Neonatal Emergency Transport Service (STEN) adapt to modern care needs expanding its sphere of competence to children with an age of one-two years [7]. Actually it must also be considered that over time there will be a gradual reduction in the number of high risk neonate transports due to the increasing centralization of at-risk pregnancies, and at the same time there will be an increase in requests for the transportation of critically ill children to the hub hospitals. The Study Group of intensive care in early childhood (TIPI: *Terapia Intensiva Prima Infanzia*), set up within the Italian Society of Neonatology (SIN), is a point of reference for all neonatal doctors and nurses who are involved in intensive care of infants and who are looking for information and tools to carry out their work and wish to develop a network that encourages cultural exchange between professionals in this new and developing field.

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LECT 14

MANAGEMENT OF SEPTIC SHOCK IN NEONATES

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INTRODUCTION

Septic shock is an inadequate tissue perfusion condition secondary to cardiovascular dysfunction occurring in suspected or certain sepsis, requiring fluid resuscitation or inotropic support, associated with high morbidity and mortality. The risk factors are the same as in sepsis. Causative organisms are gram positive, gram negative, less common viruses and fungi. Septic shock is a dynamic process. In the early compensated stage blood pressure (BP) and cardiac output (CO) are maintained, skin is perfused (warm shock). Later, increased afterload impairs CO, oxygenation and systemic blood flow decrease, extremities become cold, prolonged refill time is observed (cold shock). Despite peripheral vasoconstriction, hypotension occurs resulting in the worsening of the clinical conditions.

RECOGNITION OF SEPTIC SHOCK

Early recognition of septic shock is crucial to save lives. Clinical diagnosis should be made before hypotension occurs. The main signs are tachycardia or bradycardia, tachypnea or apnea, poor peripheral perfusion, refill time > 2", decreased urine output. Besides the common laboratory tests procalcitonin revealed superior to C reactive protein for diagnosis, with regard to the severity course of infection. High sTREM-1, E-selectin and low Mannose-binding lectin serum levels show a negative prognostic value. Metabolomics is a potential technique for early diagnosis and outcome prediction, due to the perturbation of metabolic response occurring in septic shock. Minimal invasive testing and functional echocardiography are considered necessary to target treatment.

MANAGEMENT

If septic shock is suspected, action is required as soon as possible because each hour of delay doubles the risk of death. The progression of shock

must be blocked within 1 hour by optimizing the perfusion and the delivery of oxygen and nutrients to the tissues. In neonates septic shock may be a primary condition, or secondary to cardiac failure, commonly associated with systemic pulmonary hypertension, hence therapies include volume resuscitation, inotrope support and right ventricles afterload reduction, following guidelines set by The American College of Critical Care Medicine (see Dellinger et al.). Establishing an airway and obtaining peripheral or central venous access are the first steps in the management of a septic shocked neonate (0-5 min). To maintain and/or restore adequate tissue perfusion in terms and older preterms infants, an aggressive volume expansion is allowed (20-40 mL/kg up to 60 mL/kg). For VLBW neonates a single bolus of 10-20 mL/kg over 30-60 min is recommended because of the risk of IVH, heart and/or pulmonary overload. Use of inotropes is indicated when myocardial contractility remains compromised despite volume replacement. Dopamine is the first-line agent. Dobutamine is useful in case of myocardial dysfunction and high peripheral resistance. In fluid-refractory, dopamine-resistant shock, epinephrine should be used (0.05-0.3 µg/kg/min) or if shock is not reversed with low BP, norepinephrine (0.05-0.5 µg/kg/min) or vasopressors are needed. A delay in the administration of inotropes increases the risk of mortality of 20 times. In neonates unresponsive to these interventions with cold shock, normal BP and left ventricle dysfunction, a vasodilator is needed. The presence of right ventricle dysfunction and PPHN needs inhaled nitric oxide (NO) to reduce right afterload. Milrinone, inhaled iloprost, or adenosine can also be used. Empiric antibiotics should be administered within 60 min. Prostaglandin should be administered until ductal-dependent congenital heart disease is excluded. Correction of hypoglycemia, hyperglycemia and hypocalcemia should be done if needed. When shock is not reversed, in severe compromised condition, extracorporeal membrane oxygenation is life saving. In preterms infants hemodynamic responses are variable and difficult to interpret. Refractory hypotension may be related to PDA or IVH. Vasodilation seems a more prominent feature of cardiovascular failure than myocardial dysfunction, apparently alike to adults.

ADJUNCTIVE TREATMENTS

Vasopressin (VP) and terlipressin (TP) are alternative and/or complementary vasopressors in catecholamine-refractory shock, successfully used in neonates. TP is a synthetic VP analog with more

prolonged action and greater affinity for vascular receptors. Corticosteroids use is justified by adrenal insufficiency. They may act also by improving the action of catecholamines and vasoactive drugs, inhibiting NO synthase enzyme expression, or by suppressing immune responses. NO, thanks to the stabilization of macrophage mitochondria, reduces the activation of NLRP3 inflammasome and prevents septic shock mechanisms mediated by LPS, *in vivo*. Levosimendan has vasodilatory and inotropic actions with cardioprotective and anti-inflammatory effects. It can be used in addition to common inotropic agents. It has been used in very few cases. Human protein c concentrate has been used in neonates with coagulopathy sepsis related. Improvement of micro-, macrocirculatory and coagulation parameters was observed. Melatonin thanks to its anti-inflammatory and antioxidant properties is potentially available in the treatment of multiorgan failure in septic shock. Continuous renal replacement therapy was successfully performed in a newborn with sepsis and multiorgan failure, anuria CID. Recently a significant reduction of mortality in patients who underwent exchange transfusion has been reported (36% vs 51%).

CONCLUSIONS

Septic shock is a critical condition associated with high morbidity and mortality. The key elements of management are the early recognition of infection and an aggressive approach.

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LECT 15

OUTCOME OF CHILDREN WITH CEREBRAL PALSY IN A TERTIARY CENTER IN CATANIA: A CLINICAL OBSERVATIONAL STUDY

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Cerebral palsy (CP) is a disorder of movement, muscle tone or posture that is caused by an insult to the immature, developing brain, during pregnancy most often before birth. Over the past 15 years our knowledge about the diagnosis, treatment and prevention of this disorder have changed considerably, however it remains one of the most common diseases in industrialized countries and the most common cause of neuromotor disability in childhood [1], affecting about 1 in 500 neonates with an estimated prevalence of 17 million people worldwide [2] The incidence still remain constant around 2 children for thousand per years [3]. During infancy or preschool years signs and symptoms tends to appear. In general, CP causes impaired movement associated with hyper-reflexia, involuntary movements, abnormal posture, difficulty and unsteadiness of walking, floppiness or rigidity of the limbs and trunk, or some combination of these can be present. On the basis of the clinical symptom and outcome we distinguish three different forms of CP: light, mild/moderate and severe. Severe cases of CP can lead to early death in newborns, babies, infants, and toddlers. Of special concern for risk of premature death are children who experience severe spasticity, and children with quadriplegia or quadripareisis. Many cases of infant mortality are related to premature birth and very low birth weight. Studies are ongoing to clarify if the brain damage leads to premature birth and low birth weight, or whether the reverse leads to the brain damage and subsequently to the clinical signs. In these situations, though, the injury to the brain or other organs may be too great to sustain life. In some children impairment is significant when cognitive functioning, mobility, alimentation and feeding are involved. Other conditions can influence the impairment showing a various degree of the disease for example, severe spasticity in limbs can lead to contracture and frozen joints. Children with severe impairment can lead healthy

lives well into adulthood depending on management and brain, respiratory and muscular involvement. Fortunately only few children are unable to provide self-care and most can be mobile and independent, with an improvement of the quality of life and on the prognosis of the disease. People with CP often can have underlying developmental brain abnormalities. The effect of CP on functional abilities varies greatly. Some people show normal to near normal intellectual function, but others may have intellectual disabilities. Epilepsy, deafness, or blindness and other diseases may also be present. Some people are able to walk while others aren't, but till now there is not a correlation between ability to walk and intellectual disabilities. People with CP may have difficulty with swallowing and commonly have eye muscle imbalance. People with CP may have reduced range of motion at various joints of their bodies due to muscle stiffness. There are different types of CP: spastic CP; dyskinetic CP; ataxic CP; hypotonic CP; mixed CP. Only a multidisciplinary approach and the development of targeted therapeutic strategies and shared by the various specialists involved can help improve the quality of life of these children. A study conducted in 2014 by Ferrari et al. [4] noted six signs suggestive of perceptual disturbances in children with CP. These perceptual disturbances may be used not only, as a tool to identify different clinical types of bilateral CP, but also to help doctors to give a correct prognosis of the disease and to uniform it in relation to the future rehabilitations. These signs include: grimace, frequent eye blinking, the freezing posture, startle response, startle upper limbs in position, the look of the averted eyes. Infant CP covers the broadest spectrum of disorders of posture and movement of childhood. Another study conducted in 2015 by İçağasıoğlu et al. [5] confirmed as a prolonged rehabilitation treatment (24 months) significantly improve the outcome of mild and moderate forms of the PC. In this review we have evaluated the incidence of this disease in our tertiary hospital Santo Bambino in Catania, Italy.

MATERIAL AND METHOD

During the period between January 2015 and January 2016 we have screened over 2,280 neonates born in the Santo Bambino Hospital in Catania. In this study we did not include premature children (less than 35 weeks of gestation). We observed 9 (4%) children with CP, 3 males and 6 females. All children underwent brain ultrasonography, EEG, a combination of neurological (Hammersmith Neo-

natal Neurologic examination), neuromotor (general movements, test of infant motor performance, Bayley scales) and neurobehavioral examination (NICU network neurobehavioral scale-Preemie-Neuro), brain MRI, and they were followed up every 3 months for 24 months. Two children had a severe form of CP, 3 a mild-moderate and 4 light. In all children the ultrasonography showed various degrees of PVL and IVH according to the criteria of Papile et al. [6]. EEG findings demonstrated slowing in the centrotemporal left derivation in 2 cases and the presence of spike and polyspike in the right frontal region with tendency at the diffusion in 1 case. Brain MRI showed enlargement of the lateral ventricular in 6 of the 9 cases, with asymmetry in all cases. All these children underwent a prolonged rehabilitation treatment (24 months) that significantly improved the outcome of light and mild-moderate forms of the CP. The wide range of symptoms associated with CP poses difficulties in patient assessment and in giving the right therapy also rehabilitations. In conclusion the outcome of children with CP is difficult to predict because it is related to etiological cause of the CP and also to intrinsic factor of the children. As a future direction more homogeneous studies are needed (e.g. rehabilitation treatment was not homogeneous in our study) to be able to apply results to the whole population of children with CP.

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LECT 16

QUALITY OF LIFE PERCEPTION IN EX PRE-TERM CHILDREN

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Over recent decades, as the survival rate of children born with a very low birth weight (VLBW) has improved, it has become apparent that traditional parameters such as mortality and morbidity are, by themselves, insufficient to capture the full impact of prematurity on the lives of survivors of preterm birth and their families. Quality of Life (QoL) is increasingly recognized as an important parameter to be used for measuring the validity of medical care, in follow-up studies and treatment decisions in pediatric populations. Moreover both the FDA and the European Medicines Agency strongly recommend the inclusion of quality of life assessment as an end point in clinical trials, regardless of patient age. QoL is a construct related to the individual's perception of his/her situation in life, in particular within the cultural setting and system of values in which he/she lives and in relation to his/her own expectations, aspirations and interests. Consequently QoL is determined by physical, social and emotional aspects that are important and relevant to the individual: it is a purely subjective point of view. Although it is generally assumed that impaired physical function and disease severity are the main factors impacting negatively on an individual's QoL, there is no evidence that having a biological impairment automatically translates into a poor self-assessed QoL, and this is particularly true in children. There is a correlation between QoL and health, functional status and degree of disability, but they are not synonymous. Although QoL is a very important parameter, precisely because it is a subjective measure of well-being, it is very difficult to measure in young children. Indeed, in pediatric populations, the assessment of QoL is complicated by developmental considerations and by doubts over the acceptability of parent-proxy ratings: most of existing instruments are questionnaires addressed to parents, teachers or doctors and we know that a proxy's perception may not be an accurate reflection of how the child is functioning or feeling. Furthermore most available QoL questionnaires use written questions: this implies that whoever completes them have to read and understand the questions and there exist problems with younger children and with subjects with learning disorders or mild cognitive disability. Moreover, most available inventories highlight only negative feelings (how

angry or sad the child feels; how hard or difficult he/she finds it to do something because of the disease, and so on), an approach that could influence children's answers negatively, and seem to suggest depressive situations. Starting from the real need to develop a child-oriented QoL assessment methods designed specifically for VLBW children at school age, we developed a new self-report tool, called SOLE VLBWI Questionnaire (SOLE VLBWI Q), thanks to a multicenter project founded by Mariani Foundation of Milan. This instrument uses a multidimensional, child-centered approach, appropriate language and a modality (illustrations, emoticons and stickers) that is suitable for and appealing to children aged 6-10 years. In developing our new instrument a considerable attention was devoted to focus group with VLBW children, with the aim to obtain valuable information directly from the children's point of view about their tastes, the games they like to play, the most important parts of their day, and above all their particular perspective. All this information proved particularly useful for the subsequent construction of the questionnaire. The final version of the questionnaire consists of a set of pictures showing different everyday situations, typical of childhood. In each illustration, the child is required to fill in the face of the protagonist (a girl/boy ideally representing herself/himself) using stickers with emoticons, which correspond to how the child "feels" in the given situation (sad, neutral or happy). A novel feature of our new questionnaire compared with the approach adopted in most instruments aimed at children is the fact that oral language is used minimally. Indeed, participants are not asked questions verbally, but rather, on the whole, through the use of a visual form of language, i.e. illustrations of various situations: the examiner explains each situation verbally, in brief and unambiguous terms and the SOLE VLBWI Q transforms a theoretical concept into something absolutely concrete. Every effort was made to ensure that the child was able to identify with the protagonist depicted in the illustrations. Indeed, each child, before starting the test, is required to select, from a face gallery, the face that he/she feels best represents him/her. In each picture, the face of the protagonist is left blank (a white circle) and the child can complete the picture by applying the sticker that best illustrates his/her mood in the given situation. Every effort was made to depict the contents of the scenes in a neutral manner, so as to leave the child free to imagine himself/herself as the character depicted, and so as not to influence

his responses. The characters in the pictures are stylized and shown from the waist up so as not to create difficulties for children with motor problems. With the collaboration of colleagues participating in the SOLE VLBWI Q Study Group, we have recently validated this new self-report tool and it is in our opinion an useful instrument for collecting, in a neutral way, a primary school child's account of his/her life. We propose SOLE VLBWI Q as a new tool for assessing QoL in preterm children during follow-up at age 6-10 years.

ACKNOWLEDGEMENTS

The financial support of Mariani Foundation of Milan (Grant n. R-10-83) is gratefully acknowledged.

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LECT 17

OXYGEN SATURATION TARGETS AND RETINOPATHY OF PREMATURITY IN ELBW INFANTS

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BACKGROUND

Optimal oxygen saturation (SpO₂) targets for extremely preterm infants in the postnatal period beyond the delivery room remain controversial. Oxygen therapy in these infants should balance the benefits of tissue oxygenation and growth with the risks of oxygen toxicity. Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina occurring mostly in newborn preterm infants of which O₂ has been shown to be a key mediator.

ROP first appeared in the '40s [1], when it was called retrolental fibroplasia (RFP). During the '50s about 10,000 newborn infants were diagnosed to suffer from this condition. Since this first epidemic, due to unmonitored O₂ supplementation given to term infants in US and Europe, a second epidemic occurred in developed countries in the late '90s, now facing extremely low birth weight (ELBW) infants. A third epidemic is now taking place in developing countries, such as India and China, characterized by severe ROP in bigger premature babies. Again, improper O₂ administration is the leading reason for it. To investigate on relationships between O₂ and ROP, in the '80s and '90s oxidative stress effects on preterm infants have been extensively studied, and it became clear that not only high O₂ concentrations, but also hypoxia/re-oxygenation episodes, through free radicals production, may cause ROP. Through the same mechanisms O₂ administration is a risk factor for brain injury, bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC). Today ROP has become the most common cause of preventable childhood visual impairment and blindness throughout the world.

PATHOPHYSIOLOGY OF ROP

Retinal vascularization starts around 16 weeks gestation. Retinal blood vessels extend out from the optic nerve and grow peripherally. Vascularization in the retina is complete between 36 weeks (nasal retina) and 40 weeks (temporal retina). In preterm infants retina maturation may be delayed until 48 to 52 weeks postmenstrual age (PMA). The pathophysiology of ROP has been described in two phases. Phase I ROP or vasoconstrictive phase occurs immediately after birth during exposure to hyperoxia. This is characterized by vasoconstriction and obliteration occurring predominantly in the developing retinal vessels, secondary to a marked decrease in vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1). During this phase suppression of the normal anterior ward vascularization of the retina is also observed. Phase II ROP or vasoproliferative phase begins around 33 weeks' and occurs during the weaning from O₂ to air. It involves dilatation and tortuosity of the larger vessels in vascular retina and neovascularization and proliferation of new vessels from avascular retina into the vitreous. During this phase, VEGF levels increase, especially if there is retinal hypoxia with increasing retinal metabolism and O₂ demand. Neovascularization may cause retinal edema and hemorrhage. Moreover, abnormal fibrovascular tissue may develop and later contract,

producing traction on the retina. In the most severe cases, retinal distortion or detachment may occur. However, in most instances, the abnormal vascular tissue regresses with little residual effect. Indeed, ROP studies suggest that infants born at ≥ 32 weeks are not at risk of suffering from the disease and most infants born at > 28 weeks who develop ROP have a mild form.

OXYGEN SATURATION TARGETS AND ROP

Pulse oximetry is now the most commonly used method of monitoring oxygenation. It allows to continuously and non invasively titrate O_2 administration to infants. In adjunct, recently near-infrared spectroscopy (NIRS) has been shown to be a reliable monitoring technology for retinal oxygenation [2]. Prevention or early treatment of ROP involves careful monitoring of O_2 administration through pulse oximetry. Nevertheless, the optimal SpO_2 target in extremely premature infants is still debated. Most of the large trials have focused on either low SpO_2 (85-89%) or high SpO_2 (91-95%) targets for preterm infants < 28 weeks, from birth to 36 weeks' PMA. A meta-analysis and systematic review of 5 RCTs on this topic showed that although the incidence of severe ROP decreased significantly among low target saturation infants, predischarge mortality and NEC were higher [3]. A big concern among worldwide neonatologists derived from these results, leaving the uncertainty about optimal SpO_2 levels to be targeted in the NICU. Recently, results from this previous meta-analysis were methodologically reassessed taking into account the quality of evidence to support the estimate of effects for each outcome [4]. Although NEC was confirmed to occur less frequently in the liberal oxygen group, no significant differences were confirmed in death or disability or neurodevelopmental outcomes at 24 months, BPD and ROP. A proposed different approach to prevent ROP is the use of graded SpO_2 target during the two different phases of the disease, low SpO_2 target during phase I and high SpO_2 target during phase II [5]. Results of the STOP-ROP trial, published in 2000, involving 649 infants with pre-threshold ROP, showed that supplemental oxygen at pulse oximetry saturations of 96% to 99% did not cause additional progression of pre-threshold ROP but also did not significantly reduce the number of infants requiring ablative surgery. However, supplemental O_2 increased the risk of adverse pulmonary events [6]. Recently, the effect of higher (91-95%) and lower (85-89%) SpO_2 targeting on retinal blood vessel growth in preterm infants was investigated. RetCam images of infants enrolled in

the BOOST-II UK trial were evaluated and a trend ($p = 0.055$) towards reduced retinal blood vessel growth among high target saturation infants was reported [7]. Finally, Cayabyab et al., in a recent retrospective study, reported that in preterm infants born at < 28 weeks and with birthweight $< 1,000$ g, saturation targets 83-89% until 32 (6/7) weeks, 90-94% until 35(6/7) weeks and $> 94\%$ at ≥ 36 weeks of postmenstrual age (PMA), decreased severe ROP and need for laser therapy, without increasing mortality compared with standard saturation target 90-94% from birth to 35 (6/7) weeks PMA [8].

CONCLUSIONS

Clinical studies on oxygen use and ROP show that changes in oxygenation may cause concerning events within the developing retina of preterm infants. It is clear that oxygen must be used judiciously in preterm infants. Further trials should focus on the above proposed approaches to prevent ROP.

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LECT 18

PROTOCOL FOR PREVENTION OF SUDDEN UNEXPECTED POSTNATAL COLLAPSE

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The guidelines of the American Academy of Pediatrics (AAP) encourage breastfeeding and promote the bonding between the mother and her healthy newborn in the immediate post-partum period [1, 2]. This “sensitive” period is crucial for the development of an intimate and profound bond of mother-infant attachment and facilitates the transition to extrauterine life, stabilizing the cardio-respiratory activity of the newborn, regulating body temperature, helping to maintain blood glucose in the normal range and modulating the behavioral and motor status. Moreover, it is widely recognized the benefit of this practice in initiating an early and lasting breastfeeding and encouraging the production of breast milk [3, 4]. For these reasons the AAP suggests that healthcare personnel should not interfere with the mother and child in the first two hours of life and during the first lactation [1, 2]. Recently, several case reports and surveys highlight

the risk of Sudden Unexpected Postnatal Collapse (SUPC) during the foetal-neonatal transitional period, corresponding exactly to the skin-to-skin contact period. SUPC is a rare disease (~ 5/100,000 live births [5]) but may lead to death or long-term neurodisability: the subjects at higher risk of SUPC are the infants of primiparous mothers; these infants undergo a period of skin to-skin contact, often lying in a potentially asphyxiating prone position on the chest or on the arm of their mothers [6, 7]. Given the undeniable benefits, neonatologists should continue to encourage skin-to-skin contact irrespective of the risk of SUPC but it is mandatory to follow precise rules to prevent SUPC [8-10]. After a careful review of the literature, the Lombardy Section of the Italian Society of Neonatology has drafted a protocol for the prevention of situations and behaviors that expose the baby to the risk of SUPC during skin-to-skin contact in the first hours after birth. The purpose of this protocol is to help the Obstetricians and the Neonatologists in the proper observation of the newborns during the transitional period when the attention of the personnel healthcare is sometimes reduced. Below we summarize the main points of the protocol.

ROLES AND RESPONSIBILITIES

Local health services (public, private, accredited and non-accredited) and those who stand by during and after the delivery should inform the pregnant woman about the risk of postnatal collapse. Considering the rarity of the event, the risk of postnatal collapse must not be emphasized and appropriate words must be used; the healthcare personnel should stress that the continuous observation and the proper position of the newborn during the transitional period are mandatory.

Birth centers (local health administration/directors/head nurses):

- must make available material and equipment necessary for the correct course of activity in the delivery room;
- should ensure that staff observing the newborn in the delivery room is adequately trained;
- must make available proven procedures in case of emergency.

Head nurses must ensure:

- the procedures to promote or support skin-to-skin contact and follow the criteria of safety and suitability of the delivery room;
- an adequate environment (privacy, temperature, noise control, light);
- well-trained staff;
- protocols in place;

- availability of pulse oximeter (even though pulse oximeter is used routinely in many hospitals to monitor arterial saturation of hemoglobin, heart rate and respiratory function, pulse oximetry monitoring is not recommended under physiological conditions but can be considered in selected situations: e.g. absence of reliable relative, reduced healthcare personnel, work overload);
- newborn evaluation form.

Midwives or Pediatric Nurses must check and fill in the evaluation form:

- the correct position of mother and infant;
- that mother and child are never left alone (staying with staff and/or family members);
- that the personal electronic devices are switched off (the use of cell phone or other devices causes lack of attention).

The evaluation of the newborn parameters in the first two hours of life must be recorded in the newborn evaluation form by observing healthcare personnel:
Timing: at 15' – 30' – 45' – 60' – 75' – 90' – 105' – 120'.

Position: newborn must be prone, with the head turned towards the mother's face so that the mouth and nose are visible and not blocked by the breast or by secretions.

Skin color:

- Normal: pink skin – acrocyanosis – pseudocyanosis;
- Pathological: pale skin – central cyanosis – pale skin plus central cyanosis.

Respiratory rate (RR):

- Normal RR: 30-60 breaths/minute;
- Pathological: RR < 30/min or > 60/min – Apnea – Dyspnea.

Heart rate (HR): normal > 100 beats/min.

Reactivity/Tone: response to environmental stimuli/flexed limbs.

Skin temperature: 36.5-37.5°C.

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LECT 19

HOME BIRTH: THE RISKS OF AN ANCIENT PRACTICE

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The debate inherent the safety of home birth versus hospital birth is one of the most controversial issues in perinatal medicine and is yet to be resolved. The Australian and New Zealand College of Obstetricians and Gynecologists oppose home birth; of a different opinion are the Royal College of Obstetrics and Gynecology and the Royal College of Midwives in the United Kingdom, the Australian, New Zealand and Canadian College of Midwives that support home birth in uncomplicated “low risk” pregnancies. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists affirm that hospital and birthing centers are the safest settings for birth in the US while respecting the right of the woman to make an informed decision about delivery. The Canadian Society of Obstetricians and Gynecologists recognize the need for further research. Home

births, despite showing a decreasing trend in the last 10-15 years, are widespread in the Netherlands, consisting of about 25% of total deliveries. The Dutch obstetric system due to medical, economical and organizational issues, does not consider the low risk pregnant woman as a patient and, as long there are no complications, midwives supervise their entire pregnancy, perform all checks and attend the birth at home. These low risk women can also choose to deliver in a hospital obstetric unit with the midwife supervision but will be additionally charged for hospital bills. Pregnant women are referred to an obstetrician only in specific cases if any complications during pregnancy or delivery arise. In contrast to what is happening in the Netherlands, over the last few decades many developed countries experienced sharp rises in home birth rates. While the number of home births in most of these countries remains low (US 0.6%, UK 3%, Sweden 0.1%) the trends are striking: for example, home births in the United States increased by almost 30 percent between 2004 and 2009 [1]. Similarly, the fraction of home births in the United Kingdom almost tripled between 1990 and 2006 [2] and out-of-hospital births in Canada more than quadrupled between 1991 and 2009. Some of the reasons of this rising popularity rely on the evidence that birth is a natural process, delivery at your own home surrounded by your relatives is much more comfortable compared to the hospital setting and fewer maternal interventions (episiotomy, operative vaginal delivery, lacerations, cesarean sections) are administered in planned home birth compared to planned hospital birth. The safety of home delivery in low risk pregnant women is supported by a body of data coming from areas of the world where this practice is common like the Netherlands or Canada [3, 4]; in these countries all the medical and organizational aspects of home delivery are strictly regulated by the health care system and perfectly integrated with him. Conversely other reports show a worrisome increase in neonatal mortality or morbidity compared with hospital birth [5, 6]. It needs to be emphasized that, also in the ideal settings where home delivery is extensively diffused, there is a substantial proportion of low risk women who planned to give birth in a non obstetric unit that necessitate of an hospital transfer due to non preventable complications arisen during or after delivery; this event is particularly frequent in nulliparous woman with an incidence of about 40% of deliveries, less frequent (10%) in multiparous women [7]. High quality evidence to clarify this

debate is limited due to the absence of randomized clinical trials of planned home birth, consequently the information available comes from observational studies that are affected by methodological limitations: small sample size, lack of appropriate control group, difficulty in making a distinction between planned and unplanned home births, heterogeneity in the skills or training of the birth attendant. Irrespective of personal beliefs, women aiming for home birth should be honestly counseled about its risks and benefits based on the best available scientific evidence possibly adapted to the specific health care system or region where delivery should occur: outcomes derived from studies on a specific population may not apply to other regions or countries where the medical and organizational aspects of maternity care are provided very differently. Specifically, they should be informed that planned home birth might be a reasonably safe option if adequately selected to be at low risk of complications, being multiparous and cared for by appropriately trained, qualified and licensed midwives. They should also be informed that home delivery needs to be integrated in a system that guarantees the possibility of a timely transfer to an institution with adequate skill in caring for maternal and newborn health should any complications arise. Women should also be informed that although the absolute risk may be low, planned home birth is variably associated with an increased risk of neonatal morbidities when compared with planned hospital birth.

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LECT 20

NEONATAL ULTRASONOGRAPHY SCREENING

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The wide availability of ultrasonography screening as a harmless, efficient, and apparently easy instrument, has led, over the years, to an exponential increase in the number of neonatal tests, as well as to the realization of ultrasonography screening programs finalized to the early diagnosis of various congenital malformation pathologies (specifically of the urinary tract and skeletal system). Actually the implementation and diffusion of every screening must be duly justified, and therefore, it is unavoidable to refer to Wilson's 10 classical criteria [1]. The application of these criteria to the Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) includes knowledge of the morphological aspects, clinical development, complications, and effectiveness of treatment, which unfortunately is still incomplete. Wilson's third criterion (i.e., there should be an acceptable treatment for patients with the disease) deserves special consideration. It has been recently understood that the kidneys damage associated with CAKUT and specifically with vesicoureteral reflux is mainly of dysplastic nature; the surgical correction of the reflux does not change the natural history of the associated parenchymal lesions, even the antibiotic prophylaxis of the infectious complications has not provided evidence of its effectiveness. Moreover, it is questionable if it is appropriate, in terms of costs and correct use of the resources, to verify the accuracy of the ultrasonography tests carried out during pregnancy with a second screening test after birth. It appears more reasonable to invest in pregnancy monitoring with operators of great skill and experience, properly trained to search for CAKUT. The need to execute the screening for the developmental dysplasia of the hip (DDH) to identify at early stage all the newborns affected by this disease is widely supported. There is no agreement on the diagnostic tests and organizational modalities to be used to

implement the program. The American Academy of Pediatrics has been publishing for many years the guidelines that should be adopted in order to reduce the number of DDH late diagnoses. The most important points of these guidelines are the following:

- all newborns must be screened by physical examination; it is recommended that screening should be done by a properly trained health care provider;
- according to the new available data, ultrasonography of all newborns is not recommended;
- examine all infants' hips according to a periodicity schedule and follow-up until the infant is an established walker;
- record and document physical findings;
- it is necessary to remember that clinical signs of DDH may be absent at birth, but they can appear later;
- if physical findings raise suspicion of DDH, or if parental concerns suggest hip disease, confirmation is required by expert physical examination, referral to an orthopedist, or by an age-appropriate imaging study.

According to the AAP commission, if all the pediatricians followed these indications the number of the newborns affected by DDH identified after the first year, could be almost zero. In our country, the situation is confused as there is no screening program but a non-coordinated program of ultrasonography of the hips for all newborns. The critical analysis of this situation leads to some considerations that go beyond the discussion about the effectiveness of the ultrasonography screening:

- it is indispensable for the pediatricians to understand the need and importance of DDH early diagnosis;
- it is necessary that all the pediatricians operating in a specific geographic area jointly agreed on the organizational plan of the screening program to be implemented: diagnostic tests to be used, test schedules, results recording modalities, and adequate structures for infants who need treatment;
- the number of late diagnoses, unrecovered cases, and number of patients with iatrogenic complications must be constantly recorded;
- these data should be periodically discussed in order to evaluate if the screening program chosen has produced satisfactory or non satisfactory results, and decide if the same program should be continued or changed.

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LECT 21

PULSE OXIMETRY SCREENING FOR CRITICAL CONGENITAL HEART DISEASE IN THE WELL-BABY NURSERY

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Congenital heart disease as a group represents the most common congenital malformation in newborns with an estimated incidence of 8/1,000 live births. The most severe forms (usually referred to as critical congenital heart disease) are potentially fatal for the neonate in the first weeks of life and constitute one of the leading causes of neonatal death in the developed countries. If timely detected, most congenital heart defects can be surgically corrected or palliated. A number of studies has shown that an early diagnosis of critical congenital heart disease is associated to better perioperative condition, a shorter Intensive Care Unit stay and a better surgical outcome. At present, a significant but variable proportion of congenital cardiac malformations is detected by antenatal ultrasound screening. This is especially true for those defects that grossly alter the dimensions of the four cardiac chambers. Other defects (especially the anomalies of the aortic arch but also the transposition of the great arteries and the anomalies of pulmonary venous return) are often missed at prenatal ultrasound screening. The incidence of critical congenital heart diseases that escape prenatal detection ranges 9-25/10,000 livebirths in different studies and appears to decrease over time. It is well known that critical congenital heart disease may be asymptomatic or may present only subtle clinical signs in the first days of life and therefore may be overlooked at routine pre-discharge neonatal physical examination. Wren reported a 25-30% incidence of potentially life-threatening congenital cardiac diseases undiagnosed at the time of discharge from hospital in the Northern Health Region of England in years 1985-2004. In

more recent years a population-based study from Massachusetts found that a delayed diagnosis of critical congenital heart disease occurs in over 13% of cases. In the last decades pulse oximetry has widely spread as a screening tool for the detection of critical congenital heart disease. The rationale behind pulse oximetry is that many congenital heart defects present mild cyanosis that is hardly identified on inspection but can be detected by measuring oxygen arterial saturation. Pulse oximetry is a readily accessible, rapid, cheap, non-invasive test and it is well accepted by parents. A number of large cohort studies have evaluated to date the efficacy of pulse oximetry as a screening test for critical congenital heart disease. A meta-analysis published by Thanganatiram et al. on *Lancet* in 2012, analyzed data for 230,000 neonates who were screened with pulse oximetry for critical congenital heart disease and found an overall high specificity (99.9%; false positive rate: 0.14%) for pulse oximetry and a moderate sensitivity (75%). Factors that account for the variability in specificity and sensitivity among different protocols are the cutoff used, test timing (false-positive rate is lower when babies are tested after 24 h of birth), the exclusion or inclusion of prenatally suspected defects, the definition of the targeted critical cardiac diseases. Pulse oximetry sensitivity was found to be particularly low for coarctation of the aorta and other left ventricular obstructive lesions. Aiming to improve the detection of aortic coarctation many screening protocols adopt a double measurement site, both preductal and postductal, so that a right to left shunt across the patent ductus arteriosus could be unmasked by the difference between upper and lower limb oxygen saturation. In 2011 pulse oximetry screening for critical congenital heart disease was added to the recommended uniform screening panel in the United States with the endorsement of the American Academy of Pediatrics and the American Heart Association and is actually implemented in many of the States. According to the AAP protocol oxygen saturation is measured at both upper and lower limb. Recommended screening time is 24-48 h after birth or close to discharge if it occurs before 24 hours. Test is positive if SpO₂ is < 90% in either the right hand, or either foot or both readings are < 95% on three measurements each separated by 1 hour, or a 3% difference in the right hand and foot SpO₂ is confirmed on three separated measurements. Positive cases should be investigated promptly with echocardiography for a definite diagnosis. In Italy a

screening for congenital heart disease is not currently mandated nor recommended but some maternity hospital have implemented it on a voluntary basis. It is possible that different health policies and local situations make the results of studies carried out in other countries not fully applicable in Italy. As an example, in Italy the hospital length-of-stay is longer than in the US, the UK, and Scandinavia, and rarely newborns are discharged home before 48 hours of life. This fact may limit the risk that a critical cardiac disease is sent home without a diagnosis. Unfortunately, nationwide data are lacking on the efficacy of the prenatal diagnosis as well as on the incidence of delayed diagnosis of congenital heart disease. In a prospective study conducted in 16 Italian maternity hospitals the efficacy of prenatal screening appears to be higher than that reported in most studies from other countries. Nonetheless, a significant difference in the clinical detection rate is observed between tertiary and non-tertiary units so that, in the latter, pulse oximetry screening give a significant contribution to fill the diagnostic gap. In the same study, evaluation of the peripheral perfusion index (PI) was added to the measure of oxygen saturation to try to improve the screening sensitivity for left-sided heart obstructions. PI is a oximetry-derived parameter expressing the relative amount of arterial blood at the probe site, independent by oxygen saturation. In previous studies PI was proposed as a possible screening method for cardiac conditions presenting normal oxygenation but low systemic perfusion. Unfortunately, because of the high prenatal and clinical detection rate, the number of left heart obstructions which underwent the screening was lower than anticipated and no definitive conclusion can be drawn about the additional contribution of perfusion index to pulse oximetry screening.

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LECT 22

CRITICAL ISSUES IN THE EARLY DISCHARGE OF THE NEWBORN

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Early discharge (ED) of healthy "late preterm" and full term newborn infants has become a common practice because of current social and economic necessities. The average length of stay of mothers and infants after delivery shortened steadily from 1970 until the mid-1990s and in 1995, the American Academy of Pediatrics (AAP) defined early and very early discharge as stays of 48 and 24 hours, respectively, after uncomplicated vaginal delivery. The length of stay (LOS) of a child after birth has been a controversial topic over the past few decades. A Cochrane Review in 2002 found that early postnatal discharge showed no adverse effects on breastfeeding and maternal depression when accompanied by a policy of nursing/midwifery home visits. Even if this practice has become more and more widespread, there was an increased rate of early post discharge readmission for jaundice, feeding problems, excessive weight loss (WL), dehydration and hyponatremia. For this reason, it is recommended that early discharged neonates should be evaluated shortly after discharge. Our aim was to review the available data about the safety of ED as regards to the most common problems causing hospital readmission.

JAUNDICE

ED after birth may preclude the timely identification of a significant jaundice or its worsening, especially when a clinical inspection and/or laboratory test is not planned in the short term (24-72 hours). Not only hyperbilirubinemia is the most common cause of rehospitalization, but its most feared complication, kernicterus, is also still reported. A recent study showed how 8 per 1,000 term infants were readmitted for jaundice. Infants born at 37 weeks' GA with a LOS at birth of 0 to 2 days were over 9 times and at 38 weeks' GA were 4 times more likely to be readmitted for jaundice compared with infants born at 39 weeks' GA with a LOS of 3 to 4 days. Other significant risk factors for readmission for jaundice in infants discharged 0 to 2 days after

birth included vaginal birth, born to mothers from an Asian country, born to first-time mothers, or being breastfed at discharge.

A correct approach to this aspect includes:

- performing a bilirubin test (transcutaneous and/or serum bilirubin) in all newborns, especially if early discharged or with clinically evident jaundice;
- adopting a nomogram that allows early identification of the subjects with low, medium and high risk, even with a single sample test made after the first 24 hours of life;
- carefully monitoring of the subjects at risk.

WEIGHT LOSS AND HYPERNATREMIC DEHYDRATION

The emission of meconium and urine after birth is not compensated by adequate intakes, so that a drop in birth weight (BW) is a physiological phenomenon and not a concern. However, in the presence of some diseases such as infections, severe anemia and respiratory distress, WL can be excessive and become pathological. Causes of “non-pathological” WL are delayed breastfeeding, an incorrect sucking or limited number of feedings. It is considered as “normal” a WL up to 10-15% of the BW, that it is usually recovered within 7-10 days; however, in breastfed infants a drop of more than 7%, although not pathological, can be the indicator of the need of the mother to be trained by skilled nurses. The risks that accompany an excessive WL are the following: increasing jaundice, hypernatremic dehydration, interruption of breastfeeding.

EARLY ONSET SEPSIS

Early onset sepsis, with vertical transmission, have the remarkable frequency of about 2 cases per 1,000 births alive. The bacteria usually responsible are the Group B *Streptococcus* (GBS), *E. coli*, *Listeria spp.* These sepsis show a sudden onset, sometimes dramatic, usually during the first 72 hours. In particular 90% of GBS sepsis begins in the first 24-48 hours of life, for which an hospital observation of the children born to GBS positive women for at least the first 48-72 hours is recommended.

NEONATAL METABOLIC SCREENING

The degree of reliability of neonatal screening depends on the moment of execution of tests after birth. A discharge too early may result in lack of testing (loss to follow-up) or reduction in the sensitivity of the same. The ideal moment is between 49 and 72 hours. For ED before 48 hours, screening can be performed to prevent patient losses but it is suggested to repeat the test within 7 days of life.

CONGENITAL HEART DISEASES

Although far more rare, serious congenital heart disease (CHD) affects 0.4-0.5% of live births. The typical hemodynamic changes of the first days of life, linked to patency of the ductus arteriosus, make these pathologies recognizable at birth only in 1/3 of cases, often under multiple malformations. For the same reason the murmur is not always present and is recognized only 50% of cases. Aortic coarctation is the CHD that is most likely to show later and that should be suspected if an infant does not grow well or has trouble in breathing; in fact this disease manifests itself only after the closure of the ductus arteriosus. Pulse oximetry screening could be a useful tool to identify unsuspected CHD.

SOCIAL RISK FACTORS

The social risk factors related to the newborn can be summarized as follows: maternal addiction, history of abuse or domestic violence, mental diseases of parents, homelessness, low level of maternal education, lack of competence and/or social support, frequent in primiparous mothers, teenagers, women without partners, immigrants.

CONCLUSIONS

In conclusion, to reduce the risks associated with ED, it is necessary to create follow-up programs as much as possible individualized for the mother and for the baby. These programs should consider WL, proper breastfeeding initiation, bilirubin levels, risk factors for severe jaundice, social risk factors and the family compliance.

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LECT 23

FEVER IN THE NEWBORN: WHAT TO DO?

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Fever in the first weeks of life is a controversial clinical sign to decode, because it can be caused by many medical conditions ranging from not serious to potentially serious. Recent researches showed that about 25% of neonatal deaths worldwide are related

to infectious causes. According to the Italian Society of Pediatrics in infants up to twenty-eight days of life, the temperature should be measured axillary with electronic thermometer, both in hospital and at home. Nearly 5-22% of newborns that are visited in the Pediatric Emergency Department for fever have no signs or symptoms that can help the neonatologist to assess the site of the infection. Although fever is often caused by viruses, in 7% of neonatal patients fever it is the first sign of severe bacterial infections (sepsis, arthritis, pyelitis, urinary tract infections, pneumonia, meningitis etc.). The most important bacteria that are generally involved are: *E. coli* (39%), *Klebsiella spp.* (11%), Group B *Streptococcus* (8%) and *Enterococcus spp.* (6%). The epidemiology of etiological agents involved has changed after the introduction of the vaccination strategy. For example, in the Cincinnati Children's hospital (USA) the rate of blood culture positive for *S. pneumoniae* decreased from 1.3% of 1998 to 0.25% of 2003, after the year 2000 with anti-Pneumococcal vaccine. It's interesting, too, that in recent studies Human Herpes virus 6 affects nearly 10% of infants with fever of less than three months old. Therefore, proper management of fever must begin first of all with the involvement of the family, which must be informed about proper techniques for measuring body temperature, close observation of the most common signs of infection (excessive irritability or drowsiness, anorexia, hypotonus, jaundice, inability to suck, decreased excretion of urine, etc.), and the most appropriate interventions to be made, pending pediatric visit. Based on the scientific literature, the medical management of fever must use all the most effective diagnostic tools to identify high-risk cases of developing serious complications. To identify the patients with fever at risk of severe bacterial infections, some guidelines have been produced: Rochester's Criteria show the management of fever in the neonatal period; Criteria of Philadelphia relate to children between 29 and 56 days of life; Baraff's Criteria have been theorized as practical guidelines for the management of fever in infants and children from 0 to 36 months of age. In 2013, the National Institute for Health and Care Excellence (NICE) has published new guidelines on the assessment and initial treatment of infants with fever under 5 years old. For children less than 3 months of age they recommended strictly observation of clinical signs and symptoms such as heart and respiratory rate. So it is recommended to proceed with laboratory tests: blood count, white blood cell count, differential leucocyte count, assay of levels of acute phase

proteins (for example, C-reactive protein), blood culture, urine exam and urine culture or even fecal culture when coexists diarrhea. In addition, a lumbar puncture should be performed as soon as possible when neurological symptoms appear, before starting antibiotic therapy. Chest X-ray should be performed when respiratory distress appears because it provides important evidence of lung infection. It is also important to highlight that all cases of fever in babies up to twenty-eight days of life need to be hospitalized to avoid delays in treatment and therefore the risk of serious complications. Treatment to reduce fever is generally not required. Treatment of associated pain and inflammation, however, may be useful. Medications such as ibuprofen or paracetamol may help regarding this as well as in lowering temperature. Paracetamol is the only antipyretic drug that can be used starting from the neonatal period. It is effective, well tolerated and must be used at standard weight-based dose. Ibuprofen may be used only after the third month of life starting from 5.6 kg of body weight. Measures such as putting a cool damp cloth on the forehead and having a slightly warm bath are not useful. Paracetamol is preferably administered orally because absorption rate is more constant and it is possible to achieve greater accuracy when dosing according to body weight. Without antibiotic treatment, many young infants will rapidly develop into severe bacterial sepsis, which may prove fatal. In fact it is known that the typical neonatal immune deficiencies may be responsible for a rapid evolution from infection to dramatic clinical presentations (septic shock, meningitis), often with unfavorable outcome. During hospitalization empiric antibiotic therapy has to be started especially in the following cases: babies under 1 month of life, babies between 1-3 months with poor clinical condition or babies between 1-3 months with less than 5,000 leukocytes or more than 15,000 leukocytes. Regarding the choice of antibiotic therapies, the use of a third generation cephalosporin is recommended (e.g. Cefotaxime) plus an antibiotic active against *Listeria spp.* (e.g. Ampicillin or Amoxicillin). The need for procedures designed to achieve early intervention and targeted therapy, particularly for cases at high risk of complications, makes this topic of particular interest.

LECT 24

CYANOSIS IN THE NEWBORN

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The word “cyanosis”, derived from the Greek word *kýanos* that indicates dark blue, refers in the clinical practice to the bluish discoloration of the skin, nail beds and/or mucous membranes. It can be detected by the human eye when the arterial blood level of de-oxygenated hemoglobin is 3-5 g/dl, although in the neonatal period factors such as skin color, exposure to light, or presence of jaundice can make its evaluation difficult. Recognizing cyanosis is important because it suggests an insufficient oxygenation of peripheral tissues and it is one of the clinical signs that best identify severe illnesses in infants during the first two months of life [1]. It is important to distinguish cyanosis from hypoxemia and hypoxia. In fact, hypoxemia occurs when PaO_2 is lower than the normal range (80-100 mmHg) and is commonly associated to low values of pulse oximetry ($\text{SpO}_2 < 95\%$), while hypoxia occurs when there is a failure of peripheral tissues inducing the anaerobic metabolism and the development of metabolic acidosis. Cyanosis, hypoxemia, and hypoxia are interrelated but each can occur independently from the others, and the value of SpO_2 at which cyanosis is visible depends on the hemoglobin concentration. An infant with cyanotic congenital heart disease (CHD) could be hypoxemic but not cyanotic and hypoxic when cardiac output and/or hemoglobin compensatory increase occur. On the other hand, an infant may exhibit a normal SpO_2 and evidence of tissue hypoxia in the case of impaired cardiac function and/or anemia. For example, an infant with hemoglobin of 20 g/dL will exhibit cyanosis at a SpO_2 of 80% (20% of 20 g/dL is 5 g/dL of deoxygenated hemoglobin), whereas an infant or a child with hemoglobin of 10 g/dL will not exhibit clinical cyanosis until saturation drops to as low as 60% (40% of 10 g/dL is 4 g/dL of deoxygenated hemoglobin) [2]. Thus, anemia can mask the development of hypoxemia and clinical cyanosis may become apparent only when SpO_2 drops below 85%, and cyanosis is frequently discovered during episodes of crying or feeding, when the SpO_2 decreases further [2]. Therefore, the measurement of SpO_2 plays a very important role in the screening for CHD and the American Academy of Pediatrics (AAP) recommends it in all neonates before discharge from the nursery [3]. A finding of $\text{SpO}_2 < 95\%$ in a lower extremity after 24 hours of life is an indication for further evaluation [3]. In fact, $\text{SpO}_2 < 95\%$ is considered to represent hypoxia

and at this cutoff value it reaches a specificity $> 99\%$ and a sensitivity of 75% for the detection of hypoxia, although parents and caretakers should be informed that SpO_2 cannot detect all cases of CHD [3]. Thus, the actual objective of the clinician is to detect hypoxemia, and this can be currently pursued either by low SpO_2 in case of mild/moderate hypoxemia or by low SpO_2 and/or clinical cyanosis in case of moderate/severe hypoxemia. However, pediatric patients with suspected cyanosis should be referred promptly to a pediatric cardiologist or pediatric pulmonologist as dictated by clinical situation [2]. Cyanosis can be classified on the basis of the extent of involvement in acrocyanosis (usually a benign condition), central cyanosis (usually a severe condition), differential cyanosis (when cyanosis is more pronounced in lower limbs than upper limbs; this condition is virtually diagnostic of CHD), and reverse differential cyanosis (when lower limbs are less cyanosed than the upper limbs) [4]. Moreover, cyanosis can be classified on the basis of its etiology as caused by pathologies of the respiratory system, cardiovascular system, hemoglobinopathies, or other causes (i.e. sepsis, hypoglycemia, polycythemia, central nervous system depression, apnea of prematurity, etc.) [4]. The clinical approach to a neonate with cyanosis begins with an accurate anamnesis that can contribute to address the diagnosis. The physical examination is very important because it can evidence signs and symptoms of respiratory disorders (i.e. polypnea, dyspnea), cardiovascular illnesses (i.e. murmur, abnormal pulses), neurologic pathologies, or other disorders. The measurement of SpO_2 is an excellent non-invasive tool for monitoring oxygen saturation and its evaluation in the right hand (preductal) and foot (postductal) is helpful in recognizing differential cyanosis. Hyperoxia test is important for confirming or excluding cardiac cause of cyanosis. It is expected that, after the administration of 100% oxygen for 10 min, PaO_2 (measured in preductal arterial blood) rises substantially if there is no right-to-left shunt. A $\text{PaO}_2 > 160$ mmHg after 100% oxygen administration makes the cardiac cause of cyanosis unlikely while a $\text{PaO}_2 > 250$ mmHg (negative hyperoxia test) excludes it. A $\text{PaO}_2 < 100$ mmHg (positive hyperoxia test), and/or a rise of less than 30 mmHg in the absence of lung pathology is virtually diagnostic of cyanotic cardiac cause with the exception of infants with pulmonary hypertension [4]. All cyanotic infants must be studied with an electrocardiogram. This exam is useful for the diagnosis of cardiac

arrhythmias, but has a limited sensitivity for the diagnosis of CHD. Nevertheless, some patterns are strictly related to certain cardiac malformation (i.e. left axis deviation due to left ventricular hypertrophy, which would strongly suggest tricuspid atresia [TA]) [5]. Similarly, chest X-rays do not have a great sensitivity for the diagnosis of CHD but are required for confirming or excluding pulmonary diseases, and can show cardiomegaly and/or heart appearances suggestive of specific malformations (i.e. egg on side appearance in transposition of great arteries [TGA]) [2, 4]. However, echocardiography has become the gold standard for the diagnosis of congenital heart disease and all cyanotic infants must undergo this study that allows the assessment of heart anatomy, informs on heart function, and is useful in planning and monitoring possible treatments. Infants with severe cyanosis need urgent supportive therapy while a diagnosis is established. This will include intravenous fluids and withholding of enteral feedings. Patients should be maintained in a thermoneutral environment to limit O₂ consumption, glycemia should be monitored to maintain glucose in the normal range, and acidosis should be corrected with infusions of sodium bicarbonate. A respiratory support should be considered both in infants with respiratory distress and in infants with heart diseases. Oxygen-therapy may be necessary particularly in infants with respiratory diseases and can be provided with low or high-flow nasal cannulae, continuous positive airway pressure (CPAP), non-invasive mechanical ventilation (NIV) or, in the most severe case, with mechanical ventilation (MV). It is difficult to define the most adequate PaO₂ and SpO₂ in infants, therefore the objectives of oxygen-therapy must be maintaining tissue normoxia and preventing metabolic acidosis. When patients' clinical conditions seems to exclude respiratory diseases, infants with severe cyanosis and acidosis should be immediately started on PGE1 infusion, which is effective for the treatment of ductal-dependent CHDs. There are no absolute contraindications to PGE1, although it may worsen pulmonary venous hypertension for example in obstructed total anomalous pulmonary venous connection (TAPVC), hypoplastic left heart syndrome (HLHS), mitral atresia with restrictive atrial septal defect (ASD), and rarely TGA with intact ventricular septum and restrictive ASD [4, 5]. In these cases the beginning of PGE1 infusion is followed by a worsening of oxygenation and must be promptly interrupted [4, 5]. The definitive management of infants with

cyanotic cardiac heart disease is commonly the surgical therapy, although in some case only palliative corrections are possible. In conclusion, cyanosis may be not accurate in recognizing infants with hypoxia. However, when cyanosis is present it accurately predicts a severe illness. The knowledge of its pathophysiology greatly contributes to drive the diagnostic approach and the management of cyanotic infants.

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LECT 25

HEAD TRAUMA: WHICH APPROACH IN THE NEWBORN INFANT?

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Head trauma is a relatively common event in children, accounting for more than 500,000 emergency department (ED) visits annually in US [1] and about 300,000 in Italy [2]. The highest rates of ED visits are among children 0 to 4 years old. Although traumatic brain injury (TBI) is the leading cause of death and disability in children and adolescents, the overall risk for TBI in children after blunt head trauma is low, with an estimated prevalence of TBI requiring neurosurgical intervention ranging from 0.6% to 8.3% [1]. Nevertheless, failing to detect a serious TBI can have devastating consequences. Recent guidelines on the management of minor closed head injury, released by the American Academy of Pediatrics

in 1999, distinguished children by age greater or less than two years [3]. In fact, children under two years have specific anatomic features that increase the risk of TBI: high head/body ratio, thinner head bones, greater skull flexibility, open sutures (< 1 year), higher water content, incomplete myelination and width of the subarachnoid space [4]. All these aspects may influence the dynamics of trauma and its consequences. Moreover, clinical assessment of this group could be difficult for limited/unreliable history, different era of neuromotor and skeletal development. Many studies have attempted to create accurate prediction rules [5, 6], to identify children at very low risk for TBI, thus not requiring a cranial CT scan or hospital admission. The mechanism of trauma in children under 2 years is almost always linked to accidental short vertical drop. The risk of fracture and possible TBI increases with increasing height and decreasing age. Notably, under one month of life, even low height falls (< 1 m) are usually associated with focal contact injuries (hematomas, lacerated and contused wounds). About 1-3% of short falls can cause a linear skull fracture but they are not necessarily associated with hematoma, and vice versa [7]. Of note, isolated linear skull fracture are at very low risk of TBI [8]. Falls from greater heights (> 1 m) increase the risk of death due to TBI. Although the dynamics of the trauma are not by themselves a criterion to perform a head CT scan, they could prompt the decision to observe the infant in ED for at least 24 hours [9]. Angular decelerations may cause a greater deformation of the brain and stretch compared to the linear forces, potentially causing subdural hematoma and diffuse axonal injury. This type of mechanism is linked to permanent neurological damage and is typical of the abuse [10]. On this line, when evaluating an infant under one year of age for a reported head trauma, the possibility of an abusive head trauma should always be considered, as it is the third leading cause of all head injuries in US, with an incidence of 1:3,000-1:5,000 < 1 year of age. The peak incidence (2-3 months) and rapid decrease with age of abusive head trauma are thought to be related to episodes of prolonged, inconsolable, and unpredictable crying, which are developmentally normal for infants. Deaths due to abusive head trauma also peak at 1 to 2 months of age, most likely due to higher physiologic vulnerability during early infancy [11]. Importantly, a perceived discrepancy between the type of injury and history provided should raise a concern of child abuse. Accidental head trauma may occur also in very young infants. Ruddick et al. reported their

experience on 11 newborn infants, who fell on a hard surface (hospital floor) under verifiable situations or were witnessed by someone other than the mother, during their postnatal ward stay [12]. Of note, immediate medical assessment was available for all infants. Eight out of 11 newborns had no clinical findings, while one had a temporal bruise and one a parietal swelling. Another baby, who fell from the delivery bed (about 1.2 m), had a transiently decreased level of consciousness, consistent with a mild traumatic encephalopathy. In the latter infant, CT scan revealed a fronto-parietal fracture, with a cerebral contusion underneath. Despite of the fact that hospital floors were particularly hard, clinical symptoms suggestive of underlying brain injury, such as altered consciousness or apnoea, vomiting, irritability or seizures, were absent in all babies but one, even in those with confirmed fractures. The authors concluded that even very low level falls may cause linear skull fractures in newborns. In addition, these fractures may also occur without presence of the “classical” scalp swelling, considered suggestive for this complication [12]. Indeed, their conclusions were based on a very limited number of subjects. Nevertheless, when caring for newborns or very young infants with a “minor” traumatic head injury, caregivers as well as healthcare professionals, particularly those working in pediatric or general emergency departments, should probably adopt a more prudential approach, if compared to that recommended in older patients. The threshold to admit these little infants to an observation unit should be lowered, at the same time keeping a balance between the need of a correct diagnosis and the risk of exposing them to unnecessary ionizing radiations. Further research is needed to ameliorate the performance of available predictive criteria. The aim is to better identify babies at high risk of serious traumatic brain injury, allowing prompt interventions if needed, while sparing avoidable hospital admissions or diagnostic escalation.

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LECT 26

VITAMINS AND FLUORIDE: NEW REQUIREMENTS IN A MULTI-ETHNIC WORLD

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During the last decades Italy (as Europe in general) has experienced a mass migration from countries afflicted by poverty, civil wars and religious fundamentalism. More than 5 million foreigners of about 200 different nationalities reside in Italy, forming the 8.3% of total population. In central-

northern regions the percentage is even higher (10.6% of the resident population) [1]. Over 50% of foreign residents come from other European countries (Romania, Albania, etc.). About 70,000 foreigners are pediatric subjects (0-17 years). In 2014, on a total of 8 million hospitalizations for acute care, more than 520,000 involved foreign patients (6.5%) [1]. However, there are huge variations among our regions, with hospitalization rates ranging from 0.3% in Basilicata region to 10% in Emilia Romagna region, with a highest rate in Prato province (17.5%) (Tuscany region) [1]. In this evolving panorama, pediatricians are required to be able to understand the diverse health needs of these new patients that, for age, ethnic origins, traditional customs, religious practices, level of undernutrition dramatically differ from each other. In particular, a different approach is indicated for newly arrived subjects and for long-term residents. Undernutrition during pregnancy, prolonged exclusive breastfeeding, late weaning, restricted diets, abnormal intake of tannins, and chronic diarrhea or parasitic infections are frequently observed in foreign subjects recently moved from Africa, Middle-East and Far East countries. All these circumstances contribute to a high prevalence of iron deficiency anemia, although other micronutrient deficiency may contribute to the anemic state [2]. In general, this new composite population implies for the health care provider, and in particular for the pediatrician, a specific attention aimed at evaluating different nutritional and cultural habits which may elicit new or forgotten diseases. In particular, in the last few years, great attention has been focused on hypovitaminosis D and its health consequences, especially in the pediatric population and, in particular, in those subjects at higher risk for ethnic and cultural reasons. Rickets and osteomalacia represent short-term latency manifestations of plain vitamin D deficiency. Although florid rickets is a relatively rare condition in western countries, over the past few years several papers have reported that it is resurging in Europe [3] and North America [4], in a variety of ethnic groups. Subclinical or asymptomatic hypovitaminosis D are definitely more common, even in the Caucasian population. Several epidemiological studies have shown in recent years that the prevalence of hypovitaminosis D in Italian pediatric population is very high, up to 89% [5, 6]. As for adults, the main source of vitamin D is the endogenous production in the skin triggered by the ultraviolet B irradiation. However the skin synthesis is influenced by a number of factors,

including, latitude, season, time of the day, cloud cover and pollution. In addition, individual factors, such as skin pigmentation, clothing, time spent outdoor, use of sunscreens, can strongly interfere with its natural production [7]. Very few natural foods contains substantial amount of vitamin D, so dietary sources accounts for less than 10% of vitamin status. Only fortified foods, including cereals and infant formulas or some dairy products, may account for some dietary supply. At our latitudes people at risk of developing vitamin D deficiency are all those with darker skin, e.g. people from Africa, Middle-East and Asia living in Europe, but also pregnant women and their infants with reduced sun exposure (religious and cultural reasons), infants < 12 months (especially if breastfed), subjects with restricted diets (e.g. macrobiotic, vegetarian, strict vegan), adolescents and those with a high body mass index. Finally, vitamin D levels are frequently insufficient in subjects affected by liver or kidney diseases and in case of chronic therapy with anticonvulsants, glucocorticoids and antifungal drugs [6]. There is increasing evidence that besides calcium metabolism and bone health, vitamin D has beneficial effects on several extra-skeletal tissues. The vitamin D receptor (VDR) is nearly ubiquitously expressed in a variety of tissues such as brain, heart, skin, stomach, pancreas, lymphocytes, gonads, and prostate tissue. In recent years, an impressive number of studies have been performed, on both children and adults, to investigate the preventative and therapeutic effects of vitamin D supplementation on various diseases, such as respiratory infections and flu, cardiovascular diseases, diabetes, asthma, multiple sclerosis, and cancer [8]. Furthermore, inadequate vitamin D levels during pregnancy may have short- and long-term effects on offspring health [9]. New insights on the individual metabolism are coming from studies on different VDR gene polymorphisms that may influence the vitamin D expression and activity in individuals [10, 11]. Even though specific recommendations on the adequate intake aimed at preventing extra-skeletal diseases have not yet been provided, it is mandatory for all health caregivers to look carefully to vitamin status at any age, particularly in subjects at higher risk [6]. While in industrialized countries other vitamin deficits are rare and limited to chronically ill patients or subjects with inadequate nutritional regimens (e.g. vitamin B12 in vegans), they have to be considered when approaching foreign subjects, especially if they have recently

moved from poor countries [12]. For example, vitamin A deficiency is very common in refugee children and supplementation is always indicated [13]. Vitamin B12 is another vitamin that often results insufficient in refugees [14]. Vitamin B12 occurs naturally in animal products (e.g., meat, milk, eggs), and deficiency results from inadequate dietary intake (economic, cultural and religious restrictions) or impaired absorption. Plain vitamin B12 deficiency is associated with macrocytic anemia, and occasionally pancytopenia, but it may also present with subtle nonspecific symptoms, such as fatigue, decreased concentration and memory, irritability, depression, or other neurologic manifestations. Other deficits that may be encountered in foreign children recently settled in western countries pertain to thiamine, niacin, vitamins C and E [14]. Among others, dental health represents at all ages a major health issue in both native and migrant subjects. In western countries oral health has dramatically improved since the 1960s. However, poor oral health still represents a problem in certain migrant groups. Frequently observed dental disorders include dental cavities, missing teeth, malocclusion, periodontal disease, abscesses and oral cancer. As pediatricians are responsible for the primary and often sole medical care for migrant children, they should be particularly alert to the risk of oral health problems [15]. In particular, the pediatrician must include oral examination in the daily clinical routine, educate children and their parents on reducing dietary sugar, maintaining good oral hygiene, and using topical fluoride agents (toothpaste and varnishes). After carefully assessing total daily fluoride intake, mainly via bottled or tap water (which in our country present considerable variations in fluoride concentration), oral supplements may be indicated [16]. With the same accuracy, pediatricians must be aware of the risk of acute and chronic toxicity due to excessive fluoride ingestion. Fluorosis, beyond dental disease, has, in fact, several detrimental health effects on several tissues, such as bone, heart, CNS, liver, thyroid and kidneys [17]. For this purpose pediatricians should appropriately educate parents in using a judicious amount of toothpaste, teaching kids not to swallow it, and keeping fluoride drops/tablets out of the reach of children. In this context, the toughest challenge the pediatrician has to cope with, with no doubts, is to overcome language and cultural barriers. More integrated intercultural services, especially outside the hospital, are needed; cultural and linguistic

mediators have a central role in helping the immigrants integrate in our culture and ensuring clear and effective communication between health caregivers and children and their parents.

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LECT 27

MELATONIN

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Melatonin is an endogenously produced indoleamine that mediates many physiological processes in humans, including regulation of biological clock resetting, sleep, mood, seasonal reproduction, immune response and aging [1]. The fetus does not secrete melatonin but receives it by transplacental transfer. Therefore, preterm infants are deprived of the maternal circadian melatonin secretion. Moreover, pineal hormone production is only apparent approximately 9-12 weeks after delivery, and can be even more delayed when infants are exposed to neurological insults [2]. Melatonin also functions as a highly effective antioxidant and potent free radical scavenger [1]. In the last few decades, many researchers studied oxidative stress and the use of exogenous melatonin. Newborns, especially those born preterm, are prone to suffering oxidative damage due to the immaturity of their endogenous antioxidant systems. Some research groups have carried out clinical trials in newborns with different pathologies, including perinatal asphyxia, sepsis, respiratory distress syndrome, chronic lung disease, or those subjected to surgical treatments. The results of these studies show that exogenous melatonin could reduce oxidative stress and potentially improve clinical outcomes [3-5]. In adults, the melatonin pharmacokinetic profile has been well defined. Oral melatonin is fast absorbed, but its bioavailability is much lower than that of intravenous formulation. Compared with adults and older children, in preterm infants melatonin half-life and clearance are prolonged and volume of distribution is decreased. This could be due to several factors, such as the lower body fat content in preterm infants and some drug interactions (e.g. caffeine). The half-life of melatonin in preterm babies is approximately 15 h [6]. Several animal studies have shown neuroprotective beneficial effects from melatonin treatment, both when given before and after birth. Because of its lipophilic properties, melatonin easily crosses most biological cell membranes, including the placenta and the blood-brain barrier. Clinically, melatonin appears to have potential beneficial effects in intrauterine

growth restriction and when given to children who were both asphyxiated and septic. Current evidence supports phase II clinical trials with a combination of melatonin with cooling in infants with moderate and severe neonatal encephalopathy [7]. The multiple properties of melatonin support its potential favorable efficacy in several pediatric conditions [1]. Pineal dysfunction and impaired melatonin metabolism have been associated with sudden infant death syndrome and apparent life-threatening event. Melatonin, that is supplied to the infant via breast milk according to the mother's circadian rhythm, seems to play an important role in improving sleep and reducing colic in breastfed infants compared to formula-fed ones. When children with a neurodevelopmental disorder receive exogenous melatonin, parents perceive it to be effective in alleviating sleep disturbance and in improving their behavior, as well as in restoring family functioning. Human studies found a good efficacy of melatonin in premedication for anesthesia, in sleep induction for EEG recording and in sedation of children undergoing magnetic resonance imaging when compared with placebo or with benzodiazepines. A potential protective role of melatonin on bronchopulmonary dysplasia has been hypothesized [1, 3, 4]. In order to be given intravenously, melatonin needs to be dissolved in an excipient containing alcohol or propylene glycol. Oral doses show good absorption in tissues. A neonatal intravenous formulation needs to be developed; it is unclear how much melatonin is absorbed after oral or rectal doses in infants [7]. The reported adverse effects of melatonin in children have been mild (such as dizziness, headache, nausea and sleepiness). Short-term use is safe, even in extreme doses. In animals, long-term administration of exogenous melatonin seems to affect seasonal reproduction capacity and sexual maturation. Due to this possible impact, long-term safety in children should be investigated further [8]. Promising preliminary results and the apparently favorable safety profile along with high feasibility of administration are the encouraging basis for future studies on melatonin in infants and children. Problems related to dosage, formulations (slow or fast release), and the length of treatment are awaiting solutions.

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LECT 28

IRON AND TRACE ELEMENTS

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Trace elements are inorganic elements composing human organism in minimum quantities (< 0.005%); nevertheless, they play a central role to ensure the normal functioning of nearly every biochemical process, from hematopoiesis to neurogenesis. Excessive intakes may induce cumulative toxic effects, but problems related to their deficiencies remain highly diffuse, leading to severe complications, especially during infancy. Their involvement in crucial processes such as neuro- and psycho-motor development leads to an extremely variability in short- and long-term consequences, from cretinism to subtler cognitive and relational impairments. The mammary gland has the unique ability to regulate the secretion of trace elements avoiding both deficiencies and excesses; this regulation is accomplished through various processes, involving genetic and post-transcriptional ones, acting in concert to ensure the correct secretion in milk. Elements change their concentration in maternal milk during lactation, secondarily to changes in secreted binding proteins.

The majority of them progressively reduces its presence in milk from colostrum to more mature milk, following the different baby necessities. Breastfeeding is normally sufficient to avoid deficiency in healthy term infants until 6 months of life and when breastfed, the unique real harm for the baby is represented by a maternal serious deficiency. These deficiencies are strongly related to socio-economic and cultural diversities among different geographical areas, reflecting their effect especially on population alimentary habits. In Italy the biggest risk is still represented by iron and iodine deficiency, and although several measures have been proposed, some problems still remain unsolved. Preterm babies represent a high-risk population for micronutrients deficiencies. For example, zinc levels in milk of preterm infant mothers are persistently lower compared to term baby ones. In this regard, both fortified/artificial milk and mineral integration are strongly recommended for preterm babies, even if exact daily intake and necessities remain unknown.

IRON

Iron deficiency anemia is the most well-known and common complication of iron deficiency. In newborns, important measures to avoid this deficiency are represented by delayed umbilical cord clamping and minimizing blood samples, especially in preterm ones. Iron integration in infants at risk is a widely diffuse practice, however it must be taken into account that different factors may influence such risk. Newborns from anemic mothers have lower reserves at birth resulting in a higher risk of anemia and newborns receiving erythropoietin treatment or suffering important/frequent blood loss may require a higher initial integration of iron.

IODINE

Severe iodine deficiency causes cretinism through congenital hypothyroidism. This element is involved in several developmental processes, especially central nervous system ones. For this reason, even small deficiencies are able to determine minor neurological problems in infants. The iodine intake supplementation is mandatory since the very beginning of pregnancy due to the placental passage of thyroid hormones and faster clearance. This placental passage is fundamental to ensure foetal reserves, important for future development of the baby and remains necessary during lactation. In this regard, it is strongly recommended iodized salt consumption to the general population and especially to nursing and pregnant women and infants. The importance of this measure to avoid

iodine deficiency and its harmful complications has been recently stressed through several national health institute campaigns. Nevertheless, iodized salt diffusion is still insufficient in Italy, with a rate of iodized salt not reaching the 50% of all commercialized salt and the rate of congenital hypothyroidism is still definitely higher compared to countries where an efficient prevention is widely practiced.

ZINC

This element is involved in skin keratinization, intestinal enzymes function, bone metabolism, proliferation and maturation of B, T and NK lymphocytes and neutrophils. For this reason, effects of zinc deficiency may involve a variety of organs determining metabolic acidosis, growth impairment, rickets, bronchopulmonary dysplasia and digestive problems. The widest diffused complication of zinc deficiency is represented by its specific dermatitis, highly more frequent in preterm babies. In fact, preterm infants show a lower intestinal absorption and higher urinary, fecal and cutaneous elimination and integration in subjects at risk may be considered.

CONCLUSIONS

In conclusion, it is extremely important to take into account all characteristics of microelements metabolism to identify patients at risk that may require supplementation, with an individually targeted approach rather than an *a priori* approach (**Tab. 1**). Similarly, it is mandatory to pay particular attention to women with selective alimentary habits, monitoring them and their babies for such deficiencies. It is also important, in order to avoid both insufficiencies and toxic elements presence in milk, that mothers follow balanced diets including fresh foods and avoid smoking. Last but not least, analyzing the effective application and efficacy of preventive measures applied to general population is mandatory, with special regards to preterm babies differences and characteristics.

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Table 1 (LECT 28). Recommended enteral trace minerals intakes for infants.

Trace elements	Term infants (0-6 months) Daily adequate intake recommendations	Preterm infants Recommended intake mcg/kg/day	Mature preterm human milk	Mature term human milk
Iron	0.27 mg	2,000-4,000	1.2 mg	0.3 mg
Iodine	110 mcg	10-60	107 mcg	109 mcg
Zinc	2 mg	3,000	3.4 mg	1.2 mg
Copper	200 mcg	120-150	644 mcg	252 mcg
Selenium	15 mcg	1.3-4.5	14.8 mcg	15 mcg

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LECT 29

IMMUNIZATION OF THE NEONATE

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During the last few years the percentage of target population vaccinated in Italy has significantly diminished to dangerously low levels, insufficient to ensure adequate herd immunity. Indeed, compulsory immunizations decreased from 96% to $\leq 94\%$, while the diffusion of measles, mumps and rubella vaccines are less than 85%. During the last twelve months (July 2015 to June 2016), the

number of measles cases in Italy have been 572, the highest total number in Europe, according to the European Centre for Disease Prevention and Control (ECDC) report. Almost all such cases are observed in unvaccinated subjects [1]. It is therefore of paramount importance to find the most appropriate and effective means of communication to diffuse the message of the highly favorable cost/effectiveness ratio of immunizations, and of their incomparable preventive importance both for the individual and for the society [2]. In this regard, the Italian Societies of Pediatrics and of Neonatology are carrying out several initiatives, including the use of social networking, to inform parents about the advantages of immunizations for their children, and to clarify the falsehood of the vaccine-related myths. The potential risk of side effects is quite low, however it must be very carefully considered, and the possible, even if unusual, transient or permanent contraindications must be thoroughly and individually assessed [3]. As regards the common concern about the possible induction of transient immune deficiency by vaccines, it should be emphasized that, on the contrary, the immune response is much more affected by the natural disease, such as measles, with the resulting significant increase in the overall mortality from infections in unvaccinated subjects [4]. The critical issues related to the reduced vaccination coverage concern the newborn infant; among the most important problems are the need for proper parental information, and the need of prevention in preterm infants. Indeed, vaccinations are particularly recommended in some groups of high-risk subjects, such as preterm newborns, who, due to complications of prematurity, are more exposed to the harmful consequences of infectious diseases preventable by vaccination. Preterm infants, especially those with birth weight $< 1,500$ g, may present a more pronounced and long-lasting reduction of immune

response as compared to term infants. Nevertheless, several studies, carried out to evaluate response to vaccination, suggested that they show a satisfactory response to immunization and develop protective serum antibody levels, although slightly reduced as compared to term infants. In those at higher risk, an additional booster dose may be warranted in order to ensure a response similar to that of term infants. The occurrence of vaccine-attributable adverse events (such as fever, local inflammatory reaction, prolonged crying, irritability) is lower in preterm vaccine recipients, probably due to the lower local and general inflammatory response. However, extremely low birth weight infants, particularly if immunized before hospital discharge, may show episodes of apnea, bradycardia and desaturation that resolve spontaneously in most cases. It is anyway prudent to ensure a 48-hour period of observation and monitoring after administration in these infants. Preterm infants with chronic diseases have a substantially reduced response to influenza and tuberculosis vaccines. However, the response to immunization with BCG is satisfactory if the vaccine is administered at discharge. In conclusion, according to guidelines issued by International Scientific Societies, preterm infants should be immunized following chronological age, or when a fully cardio-respiratory stability has been reached, and should receive full vaccine doses. Influenza vaccine should be given to preterm infants beginning at 6 months of age, just before and during the influenza season. In addition, either family or hospital personnel contacts of infants of less than six months of age with chronic respiratory disease should be immunized against influenza (“cocooning”). The measles-mumps-rubella vaccination, to be administered usually after 12 months of age, is also highly recommended; the vaccine could be anticipated in the preterm, in relation to the lower risk of interference by maternal antibodies, that are no longer measurable after six months of age [5]. Although there are no particular contraindications to vaccination in preterm infants, other than those considered for term newborns, it is common to observe a delay of the beginning of vaccinations, as confirmed by both Italian and foreign studies. A public information campaign is therefore highly needed, to disseminate the word on the incomparable resource available with vaccinations, and to highlight the particular usefulness in some categories of high-risk patients, such as those born preterm. Such information and education activities should be undertaken early,

already during pregnancy and at birth, and given to the family of the newborn. Finally, a common strategy at national level on the vaccination schedule in general and indications for vaccination in preterm infants in particular are also required.

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LECT 30

FERMENTED INFANT FORMULAE: EVIDENCE FROM NEWBORNS

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The intestinal tract is colonized by a complex microbial ecosystem, comprised of a total of 10^{14} bacteria. Its genome, called microbiome, encodes several functions and, as a result, the intestinal microbial commensals are considered as a functional human organ. Indeed, increasing evidence has indicated that this microbial ecosystem is implicated in several functions, such as nutrient processing, protection against infections, promotion of the immunological system, and modulation of the development of the central nervous system. The establishment of a symbiotic relationship between the human host and the gut bacteria endorses the achievement of intestinal homeostasis and the creation of a systemic healthy condition of the host. On the contrary, if an alteration in the composition

of the intestinal microbial commensals occurs, the relationship between the human host and the gut bacteria may lead to an intestinal dysbiosis and, eventually, to a condition of systemic disease. Early life represents a critical time frame during which the shaping of the composition of microbiota takes place and the relationship between the host and the microbiota is set. Accordingly, previous studies have demonstrated that infants show a microbiota profile similar to that of an adult subject within the first year of life. Colonization of the intestinal tract already begins before birth and it is affected by several factors, such as gestational age, mode of delivery, type of feeding, antimicrobial therapy. Particularly, it is widely acknowledged that breastfeeding promotes the establishment of a microbiota dominated by Bifidobacteria, enhances the protection against infectious diseases and modulates the immune development. Infant formulas, that are consumed when breast milk is not sufficient or contraindicated, although having been designed in the attempt to mimic the nutritional and non-nutritional components of human milk, cannot imitate the dynamic composition of human milk and the functional effects associated with breastfeeding. Therefore, research has focused on the identification of strategies that could enhance the biological effects of the consumption of infant formulas in order to get closer to the functional effects of breast milk. Formulas fermented with lactic acid-producing bacteria during the manufacturing process and not containing significant quantities of viable bacteria in the final product have been proposed for the prevention of infectious diseases in infancy and for enhancing the development of the infant immune system. In a randomized, placebo-controlled trial, conducted in a relatively small number of infants (n = 20), the authors have found that the consumption of a fermented formula led to an increase in the amount of Bifidobacteria and in the Anti-Poliiovirus IgA titers after Pentacoq challenge in the infants fed the fermented formula in comparison to the infants fed the standard formula. Indrio et al. have reported that healthy, full term newborns fed a fermented formula with *B. breve* C50 and *S. thermophilus* 065 for 4 months had a thymus size and fecal pH values similar to those of breastfed newborns throughout the study [1]. The clinical tolerance and the biological effects of fermented formulas, in terms of modulation of gut microbiota and inflammatory and immunological responses, have also been investigated in infants born preterm. A total of 58 infants, born with a gestational age between 30 and

35 weeks, were randomly assigned to be fed either a preterm formula fermented with *B. breve* C50 and *S. thermophilus* 065 (n = 24 infants) or a standard preterm formula (n = 34 infants) during hospital stay. Clinical tolerance of the fermented formula was good. The authors found a significantly decrease in the fecal calprotectin values for 2 weeks and an increase in the secretory IgA values in the infants fed the fermented preterm formula. No bifidogenic effect could be demonstrated with the fermented formula. The efficacy of a formula fermented with *L. paracasei* CBA L74 in decreasing the incidence of infectious diseases during winter season has been recently demonstrated in 259 infants (12-48 months) attending day care services. Specifically, in infants fed the fermented formula, a significant increase in alpha and beta defensins, cathelicidin LL-37 and secretory IgA values has been reported in comparison to infants fed a standard formula. Taking into account these findings, the role of the formula fermented with *L. paracasei* CBA L74 in modulating the development of newborns' immune system is now under investigation. At present, at Authors' Institution, a randomized, double blind, controlled trial is being conducted in a cohort of healthy full term newborns, randomly assigned to be fed either the formula fermented with *L. paracasei* CBA L74 or a standard formula, for the first 3 months of life. The immunological responses and the microbiota composition of the enrolled infants in addition to the clinical tolerance of the study formulas are under investigation. Early life represents a crucial time period in terms of programming of long-term health outcomes. Gaining further insight in the factors that affect the shaping of gut microbiota will contribute to the adequate development of the immune system and to the limitation of the occurrence of pathological conditions.

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LECT 31

LEGAL ISSUES OF NEONATAL EMERGENCY TRANSPORT SERVICE

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The Neonatal Emergency Transport Service (NETS) developed in Italy and in Europe over the last 25 years has become a cornerstone of neonatal care. In territorial realities characterized by first level birth centers without a Neonatal Intensive Care Unit (NICU), NETS is the adequate system to guarantee the transport of a pathological infant to the nearest and most adequate NICU for a tailored assistance. In addition, NETS is the joining link that allows the safe transfer of a pathological newborn from a NICU to another, for subspecialist assistance that may not be present in all NICUs (surgery, cardiac surgery, hypothermia, nitric oxide, ECMO, etc.). Specific task of NETS is to assist infants with less than thirty days of life and less than 5 kg of weight. The activity of NETS, therefore, represents a moment of extreme clinical and emotional intensity, both for the healthcare professionals on the transport team and for the doctors at the destination center, as well as for the family of the transferred newborn. In many regions of Italy NETS is an organized regional system integrated with the network of birth centers and NICU at increasingly high specialization. This results in the extreme topicality of some issues that cannot be separated from a legal implication in particular: the organization of health personnel (type of qualification, compliance with the rules on working hours), the service activation time by the arrival of transport request and transport times, the equipment (increasingly specialized over the years and with a need for its functioning to be properly verified), the safety of the vehicles used for transport (ambulance, helicopter or airplane), the cost/effectiveness report etc. About the activation time, NETS has to be ready to leave its operational headquarters in thirty minutes maximum from call. It is necessary to add to this time the duration of the journey to the calling hospital. To shorten time of transport the driver can exceed speed limit, pass through red lights, and pass vehicles even in case of overtaking ban. All these prerogatives are approved by Highway Code. As with any medical procedure, the NETS team becomes responsible for the newborn conditions as soon as it arrives at the patient' bed and it is liable for professional misconduct as well as each member of the transport team responds for the correct fulfillment of the tasks assigned. The physician of the NETS selects the most appropriate center where to hospitalize the patient as well as giving clear and understandable information to parents about the medical condition and the risks and benefits of newborn transportation. The physician also has to obtain

by parents the consent to transfer the newborn. Such consent can be waived in extreme emergency conditions. The patient's personal data are covered by confidentiality. Health records and registration of health interventions are another key aspect for legal implications that may arise in the event of litigation so it is essential that the medical record of NETS is complete of any relevant information to prove the welfare activities, thus it represents a public act and answers for forgery. In case of death at the birth center or during the transport before reaching the NICU of destination it is indispensable that the physician reports with precision the event sequence, the medical actions, the absent response and the death of the infant. In recent years in Europe forensic disputes are emerging involving the transportation of the newborn. Many of these are the result of poor communication and failure to provide adequate information to the family of the newborn. The prevention of occurrence of legal litigation needs a focus on staff training, the adequacy and continuous updating of resources and equipment, the allocation of shared operational protocols in a network involving the birth centers with their related NETS, but should also always include appropriate communication with the infant's family.

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LECT 32

END OF LIFE CARE IN NEONATAL INTENSIVE CARE UNIT

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Despite the advances in fetal medicine and the improvement in the diagnostic accuracy of many neonatal life-treating conditions that have led to an increased survival, approximately two thirds of pediatric deaths still occur in the neonatal period, most commonly in the Neonatal Intensive Care Units (NICUs) [1]. In the modern era of neonatal intensive care it is quite possible to prolong life using advanced technologies also in situation where death is both imminent and eventually unavoidable. For these cases, there is an increasing awareness of the need for guidance surrounding the decision to either initiate care and treatment with palliative intent or to begin with intensive care followed by transition to palliative care: in such cases prolongation of life may increase pain and suffering for the child as well as creating unreasonable hope and expectations in parents and families [2]. In North America, Australia and Northern Europe, the majority of deaths in NICUs follow decisions to limit life-sustaining treatment. In these units, it is rare for infants to die on the ventilator, or while they are receiving cardiopulmonary resuscitation. Some decisions to limit treatment are taken for infants who are physiologically unstable and likely to die soon regardless of decisions. However, in these countries, up to 50% of treatment limitation decisions in NICUs occur in stable infants, on the basis of predicted poor prognosis and reduced quality of life. The American Academy of Pediatrics (AAP) has advocated for a patient-centered approach when considering intensive medical interventions for newborns. Any proposed treatment must be assessed as to whether it is consistent with the child's best interests. For most ill newborns it is mandatory to clarify the prognosis before beginning the treatment. Continuation of treatment is conditional on further diagnostic and prognostic data [3]. AAP defines pediatric palliative care as treatment that aims to (1) relieve suffering across multiple realms; (2) improve children's quality and enjoyment of life while helping families to adapt and function during the illness and through bereavement; (3) facilitate informed decision-making by families and health care professionals; (4) assist with ongoing coordination of care among the clinicians and across various sites of care [4]. Since the process in neonates is increasingly related to the decision on when to initiate palliative care rather than failure of medical therapy, there is a

need for increased awareness and attention from caregivers to the ethical principles that guide such decisions. Clinical guidelines for the prevention and treatment of pain in the newborn were recently revised by the Pain Study Group of Italian Society of Neonatology, with the aim to support clinical professionals in the management and care of infants with life-limiting condition, especially when the decision of institute palliative care is done [5]. The target population is divided into two categories: 1. Extremely preterm infants (< 22 weeks) or infants with life-limiting disease in case the decision of not resuscitate is taken (anencephaly, 13 trisomy) 2. Infants with incurable disease for which a decision of withholding intensive care is matured. The lifespan of infants with terminal conditions may extend from minutes to weeks, months or even years. However care must always be tailored to individual needs of the infant and the wishes of the family. This guide covers practical aspects of infant care, including pain relief, symptom relief, comfort and dignity and how to support families during the final period of life and the bereavement. It is right to highlight the importance of a flexible approach, sensitive to parent views during the process of withdrawal or withholding of intensive support. It is important to ensure that parents have privacy, adequate time and opportunity to discuss their feeling and views with the staff. All professional roles should be involved in the process, including obstetrician and gynecologist, neonatologist, surgeon, psychologist, social worker, interpret and minister of their religion, as (appropriated) needed. Providing pain relief is important, with a preference for non-invasive drugs delivery when an intravenous line is unavailable. Comfort care with environmental and non-pharmacological interventions may also be useful. Even if it is difficult to measure pain in infants in such situation, an attempt should be made every time to personalize the efficacy of the treatment as much as possible. Again, an alleviation of symptoms such as seizures, respiratory distress, air hunger, gastroesophageal reflux, secretions should be always done. Fluids and nutrition should be tailored on the infant's need. Location of care (delivery room, intensive care, perinatal hospice) should be carefully considered and planned depending on the local organizations of care. Clinical staff requires support as well to help to balance professionalism and empathy through emotional and challenging circumstances, but this is not covered by the guidance. Medical staff must strive for effective relationship with parents and the

establishment of trust in order to guide the parents through these difficult times. Recent studies show that most parents find it helpful to share decisions to withhold or withdraw life-sustaining treatment, decisions that often precede a child's death.

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LECT 33

PEDIATRICIANS PRESCRIBING FORMULAS FOR INFANTS: SCIENTIFIC, LEGISLATIVE AND ETHICAL ISSUES

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Until the early twentieth century, the overall majority of infants were breastfed and the mean duration of breastfeeding varied from 9 to 12 months. In the following decades, however, a number of factors have significantly contributed to modify the feeding attitudes during early infancy: among these, the urbanization process together with the changing role of women in the work-family system and the development of nutritionally adequate infant formulas have certainly played a key part, ensuing in a dramatic decline of breastfeeding prevalence and duration [1]. In the Scandinavian countries, for example, the percentage of breastfed infants at 3 months of age decreased from 90% in 1930 to less than 25% in 1970. At the end of the 70s, the trend of formula feeding also spread to developing countries; in this setting, however, the unsafe hygienic conditions often led to the extrinsic bacterial contamination of infant formulas, with disastrous consequences for the pediatric population [2]. Hence, the crucial role of human milk in protecting from infectious diseases

and its short- and long-term benefits not only for the individuals, but also in terms of public health and economy, became undeniably clear [3]. In the face of this evidence, from the 70s on, the World Health Organization (WHO) has undertaken several initiatives for breastfeeding promotion and support, which, in the following decades, have allowed a progressive rise in breastfeeding rates. In particular, the training of health care personnel, the agreement between the European countries on the regulation of compositional labeling of infant formulas and the related marketing and advertising strategies [4], the Joint WHO/UNICEF Statement in support of breastfeeding [5] and other specific interventional programs, such The Baby-Friendly Initiative [6], can be included among the most successful supporting projects. In Italy, the majority of pregnant women plan to breastfeed before delivery and, actually, do initiate breastfeeding after their baby's birth: according to a national survey performed by the Italian Ministry of Health in 2014, about 96% of the babies were breastfed, exclusively or not, at hospital discharge [7]. Nevertheless, a remarkable proportion of mothers undergoes an early discontinuation of breastfeeding, mainly because of a lack of education and support towards this practice that, although natural, can be positively or negatively influenced by several factors. In addition, there are also a huge number of controversies, platitudes and not evidence-based practices surrounding the issue of breastfeeding that can contribute to its failure. New mothers, with no previous personal experience of infant feeding and often lacking family support, frequently meet serious difficulties in maintaining breastfeeding and, due to the fear of malnutrition, tend to shift to infant formulas or to introduce solid foods too early. The clinical policies routinely adopted in the Maternity wards have a major influence on the establishment of lactation; hence, despite its short length, post-natal hospital stay can either hamper or lay the groundwork for a prolonged and successful breastfeeding. In order to achieve an effective establishment of lactation, breastfeeding should be started as soon as possible after birth and provided on demand; the so-called rooming (i.e., a practice allowing mothers and infants to remain together 24 hours a day) further contributes to support breastfeeding in its early phases. Moreover, unless medically indicated, breastfed infant should not receive any food or drink other than breast milk, and the use of artificial teats or pacifiers should also be discouraged. Eventually, an adequate training of the health care staff,

focused at supporting and educating breastfeeding mothers, is fundamental [8]. In addition to the aforementioned supportive strategies, breastfeeding also needs to be shielded from possible threats, such as the occurrence of unethical practices in the trade of infant formulas. To this regard, in 1981 the WHO developed the International Code of Marketing of Breast-Milk Substitutes [9], an international health policy framework aimed at protecting breastfeeding from the commercial promotion of human milk substitutes. From a legislative view, this code does not represent a strict regulation, but it is rather an ethical tool mainly directed to health care systems, health professionals and also to mothers. With regard to the responsibility and good clinical practice of pediatric and neonatal consultants working in Maternity Units and Services, the Italian legislation establishes that the infant's hospital discharge letter should not routinely include a default line for infant formula prescription [10]. Hence, if the baby is fed exclusively with breast milk, it is strictly forbidden to suggest an infant formula firm at hospital discharge. On the other hand, in case of mixed breastfeeding or exclusive formula feeding, neither the International Code nor the Italian legislation prohibits pediatricians to suggest a specific firm or type of infant formula. Rather, in the presence of specific medical conditions (**Tab. 1**), which prevalence during hospital stay or at discharge is 17.7% [7] and for which formula supplementation might be indicated, the prescription of infant formulas should report the clinical indication for the use of breast-milk substitutes, the firm and formula type and should also include thorough instructions for its adequate preparation, as for drugs or medical devices.

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Table 1 (LECT 33). Possible clinical indications for infant formula prescription during the first days of life.

Low birth weight (< 2,500 g)
Intrauterine growth restriction (birth weight < 10 th percentile)
Large for gestational age (birth weight > 90 th percentile)
Infants of diabetic mothers
Twins
Sucking difficulties
Early weight loss > 10% of birth weight
Early hospital discharge
Explicit maternal request

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LECT 34

BREASTFEEDING PROMOTION, SUPPORT AND PROTECTION

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The Policy Paper “Healthy 2020”, proposed by the European region of the World Health Organization (WHO) to support a cross action of the government and of the public society in favor of the health and the well-being (wellness), re-affirms the necessity of inter-sectorial and integrated policies for the promotion of the community's health [1]. In this field, remarkable interest is given to the subject of the correct nutrition since the first life's stages, including promotion and support of breastfeeding, not only for the already consolidated evidences which confer to this practice a fundamental role in the prevention of important chronic diseases of the adult age, but also for the more recent evidences

(proofs) which confer to breastfeeding a relevant role in psycho-affective and relational maturation of the child and of his own family. 25 years after the campaign proposed by the WHO-UNICEF for the promotion and support of breastfeeding, notwithstanding the important interventions realized in different areas of our country and the remarkable resources employed, the results achieved are still far from the established objectives. Indeed, even though the WHO-UNICEF defined exclusive breastfeeding for children in their first 6 months of life as ideal [2], the more recent reports in our country [3] point out that, on average, at discharge only 77% of the infants are exclusively breastfed, at 4 months 31% of the infants receive breast milk, and the percentage decreases to 10% at 6 months. Even though breastfeeding rates vary significantly among different regions and different public utilities, all the available data are significantly under the standards defined by both the Ministry of Health and the WHO. To face this situation, the member states of the WHO, when defining a set of new nutritional objectives, have restarted the target percentage of exclusively breastfeeding infant at 6 months to 50% within 2025 [4]. To achieve this target, the scope of this paper is to review the strengths and weaknesses of the experiences matured in the last years for the promotion and support of breastfeeding, both in the national and local settings. It will be necessary to identify new possible areas of intervention able to better respond to the actual needs of support to the parenthood, which derive from quick and deep social changes of the last decade. To promote, support and protection breastfeeding the necessary actions can be no more limited to the unique field of the health services, but the approach will necessarily have to be multi-sectorial (multilateral) and integrated among the different social areas (social actors). Fundamental to this point will be the role that the healthcare providers, on the basis of their experiences and knowledge matured in this field, will be able to play in promoting new and efficient policies for the health, encouraging and promoting multi-sectorial interventions to integrate the different social fields. The role of the pediatrician and of the different health operators will consist in providing an important contribution to the building of a Resilient Community able to support the healthy growth of the child since the first stages of life, also in the presence of potential elements of fragility. The attention will have to be focused on the importance that the different psycho-affective, educational and relational aspects cover for the

quality and the health of the whole Community, reminding how these elements are also at the basis of that harmony of the inter-familial linkages crucial for the success in breastfeeding.

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LECT 35

BREASTFEEDING DIFFICULTIES IN THE NON-INTENSIVE CONTEXT

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The World Health Organization recommends exclusive breastfeeding for the first 6 months of life. However, in many countries (including Italy), the breastfeeding rate remains at lower levels than recommended. According to a recent survey conducted by the Italian Ministry of Health, at 5 months after birth, only 27-30% of mothers is exclusively breastfeeding. Regarding this data, it is clear that there are difficulties to support breastfeeding, and the aim of this contribution is to examine some of them. Sometimes women, during the prenatal period, are not well informed about the importance of breastfeeding and the human milk healthy properties [1]. Furthermore, maternal decision is the most important factor related to the beginning and continuing of breastfeeding. In case of gestational diabetes, obesity, or caesarean delivery, lactogenesis is usually delayed, and this is followed by decrease rate of breastfeeding. In some circumstances skin-to-skin contact after birth,

rooming-in practice, or support from hospital staff are lacking, despite being suggested by the 10 steps of the Breastfeeding Friendly Hospital Initiative [2]. Looking into more details, breastfeeding difficulties could be caused by poor lactation technique, anatomy of the infant's mouth, or maternal breast problems [3, 4], resulting in pain and difficult starting or maintaining breastfeeding. Cleft palate represents an important obstacle. It is a congenital malformation occurring during embryogenesis that can affect the lip, the palate or both. Feeding difficulties appear at birth, due to an impairment of suction and swallowing mechanisms. At this early stage, the priority is monitoring infant nutrition and weight gain [5]. There is a relationship between the amount of oral pressure generated during feeding and the size/type of cleft and maturity of the baby. For this reason, babies with cleft lip breastfeed better than those with cleft palate or both alterations [6]. In the case of complete cleft palate/lip some mothers manage breastfeeding by blocking the cleft with their mammary tissue [7]. If the diagnosis is established before birth, mothers can receive information about implication of this type of oral malformation, and they may be more willing to overcome breastfeeding difficulties. The most frequent causes of breastfeeding abandonment are lack of weight gain in the baby, easier administration of formula milk, and the refusal to breastfeed after surgical schisis repairs. Another cause of breastfeeding difficulty is tongue-tie (ankyloglossia) [8]. Although it is believed that frenotomies do not result in significant improvement of breastfeeding [9], a recent study has showed a reduction of nipple pain and latching difficulties in 75% of the mothers of infants with breastfeeding difficulties who underwent lingual frenotomy [8]. A lower rate of exclusive breastfeeding has been reported in late preterm and early-preterm infants, who are not necessarily hospitalized in Intensive Care Unit [10]. However, breast milk is the feed of first choice not only for healthy term, but also for preterm infants [11]. Breastfeeding is characterized by a better coordination between swallowing and breathing than bottle-feeding [12]. The maternal finding of poor baby weight gain and the subjective perception of insufficient milk production also account for factors that motivate the choice of formula [6]. The late preterms do not always receive the "extra" support they need or the routines practices that have a positive impact on breastfeeding, such as rooming-in, early first hour postnatal skin-to-skin contact, and withholding

the use of the pacifier [13]. On the other hand, there are maternal conditions that can interfere with breastfeeding. Breast pain can be associated to nipple rhagades, Raynaud's phenomenon and mycosis. A blocked duct, which frequently appears within the first two weeks after birth, can progress to mastitis/breast abscess [14]. The lymphatic and vascular congestion associated to interstitial edema leads to milk accumulation and engorgement. In this situation, the Feedback Inhibitor of Lactation surge contributes to involution of mammary glands. For that reason, it is important to instruct mothers to perform manual drainage and frequent breast offer [14]. In general, observation during feeding is important to detect wrong positioning of the baby and to give advice for a comfortable nursing position. Moreover, the use of cup feeding, supplemental nursing system, finger feeding, teaspoon or syringe are suggested, enhancing the newborn's ability to develop a suckling action, and facilitating the newborn's ability to self-regulate and demand food. In contrast, the use of the bottle is discouraged [15]. In the case of twins' birth, mothers prefer to feed one baby at a time. The reasons for this type of nursing are multiple: small size of babies, lack of assistance, and more equitable share mother's milk. In addition, mothers may be worried that their milk would not be sufficient for their twins. Often crying and restlessness of baby are interpreted as symptoms of insufficient mother's milk. However, the literature reports that milk production is a physiological 'demand and supply', therefore in mothers of twin babies milk production should be enough for both infants [16, 17]. In conclusion, to deal with difficulties, it is important to support and promote breastfeeding encouraging specific staff training and improving knowledge of physiology and related problems with lactation through cultural changes, review of university courses, and recognition of obstacles in the working environment.

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LECT 36

ANALGESIA FOR PAINFUL PROCEDURES INVOLVING NEWBORNS IN THE NURSERY

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The use of analgesia and sedation for invasive procedures in neonatal intensive care units (NICUs) is well documented [1], but there is a paucity of data on their use in the nursery setting. A recent

survey among Italian neonatologists has shown that non-pharmacological methods are not routinely used during painful procedures on newborn in the nursery. Even healthy newborn are often exposed to painful invasive procedures, usually involving “skin-breaking procedures” (blood sampling with heel punctures, vessel punctures to check blood sugar and bilirubin levels, or for metabolic screening, and intramuscular injections for anti-hemorrhagic prophylaxis), during which the related pain can be managed effectively using non-pharmacological analgesic techniques [2]. Most of the scientific evidence supporting the use of non-pharmacological analgesia in the newborn comes from studies on heel puncture and venipuncture, and their use is strongly recommended in this setting [3, 4]. Applying such techniques – in the nursery as well as the NICU – enables optimal pain control and expedites the procedure for the operator. The interventions concern the macro-environment (light and noise) and micro-environment (containment, swaddling, and facilitated tucking in the crib), nursing care measures, the use of sweet solutions, nutritional sucking, also in combination with various other techniques such as sensorial saturation, breastfeeding, and skin-to-skin contact. Invasive procedures should be performed with infants in an optimal baseline state of quiet vigil, not when they are sleeping (unless the procedure is urgent), or their transition from sleep to wakefulness should be promoted before proceeding. Excessive noise and bright light should be avoided to reduce infants’ stress [4]. During a painful procedure, it is important to provide containment and to have caregivers or mothers align the infants’ limbs along the midline (holding, facilitated tucking, or swaddling in bed sheets or covers) to contain their postural instability and mitigate the physiological and behavioral responses of the newborn to stress and pain, especially if they are born preterm [5]. Although there is no documented evidence available on the value of these interventions in term-born infants, their effectiveness is easy to see in clinical practice. The use of pacifiers (non-nutritional sucking) as an analgesic tool during single procedures should be encouraged. They take effect in synergy with the use of sweet solutions (sucrose, glucose, breast milk), giving rise to a rapid-onset sensory stimulation and distracting the infant from the painful stimulus. They are recommended for use throughout the first month of life [2-5]. The efficacy of sweet solutions beyond the first month of life is still debated. Among the various sweet solutions, 24% sucrose has been the

most often studied. Its efficacy and safety in reducing the pain of single painful procedures (Cochrane 2013 evaluated 4,730 infants in 57 studies) is irrefutable [6, 7]. Alternatively, 20-33% glucose has also been found effective in a recent meta-analysis (38 studies on a total of 3,785 newborn) [8]. Expressed breast milk may be administered before and/or during painful procedures using a syringe or bottle, but it seems to be less effective than other sweet solutions [9]. Several studies have examined combinations of analgesic techniques, finding that their synergic effect enhances the analgesic benefit during painful procedures [10, 11]. Whenever possible, combinations of non-pharmacological techniques – such as breastfeeding, skin-to-skin and sensorial saturation – are recommended during painful procedures in the nursery [12]. They have a multisensory stimulant action that can prompt pleasurable sensations in the infant and thereby counteract the distressing stimulus. They probably take effect through a “distraction” mechanism and the release of endogenous analgesic substances (endorphins, oxytocin). A recent meta-analysis (concerning 20 studies on heel puncture and venipuncture) pointed to a similar efficacy of breastfeeding and non-nutritional sucking associated with a sweet solution [9]. Skin-to-skin contact (or kangaroo care) is another technique used in combination with others that a recent meta-analysis (on 19 studies and 1,594 infants) found effective [13]. Sensorial saturation, which involves associating different (tactile, gustatory, olfactory, auditory and visual) stimuli that compete with the painful stimulus, helps to reduce the centrally processed sensation of pain. Voice (talking), smell and eye contact, associated with a sweet solution (taste) and tactile stimulation (massage), join forces in activating the “gate” that intercepts the arrival of the painful stimulus in the sensory and integration areas of the brain (according to the “gate control” theory of Melzack and Wall). Sensorial saturation has proved effective in reducing procedural pain (mostly from the heel pricking) in both preterm and full-term newborn; it is particularly recommended in the “three Ts” modality, involving “Touch, Taste, and Talk” [2, 14]. It may be easier to implement the above-described methods in clinical practice with the aid of checklists, which are available in the recently-published, latest edition of the SIN guidelines for the prevention and management of pain in the newborn [3]. This is a useful tool for choosing which of the various available and effective analgesic measures to adopt for a given infant. As in

the NICU, so in the nursery, it is also important to record pain scores, as measured particularly during invasive procedures – as required by Italian law No. 38/15.03.2010 (Provisions for guaranteeing access to palliative care and pain therapy).

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LECT 37

DEVELOPMENTAL CARE IN ITALY: PRELIMINARY FINDINGS FROM A NATIONAL SURVEY

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In the last decades the developmental care-oriented approach to neonatal intensive care has provided evidence of substantial effectiveness in decreasing the risk of negative outcomes in preterm infants development [1-4]. However, even if NICUs have increasingly incorporated some developmental supportive care into routine management of the infants, large variations are found in the application of procedures and programs considered as developmentally appropriate [5-7]. To our knowledge, two previous studies aimed at surveying the quality of the developmental care (DC) in Italy. De Vonderweid and colleagues [8] analyzed data from 109 Italian NICUs in 2001 and found that some basic practices, such as allowing unrestricted access for mothers or promoting breastfeeding, were poorly implemented. Greisen and colleagues [6], within a broader study on the practices of DC in Europe, studied 35 Italian NICUs. They found an unchanged situation (i.e. approximately only 30% of the NICUs allowed unrestricted access for parents) and highlighted the lower level of DC of Italian NICUs compared to the European context. The present study aims to update the previous surveys, particularly that of Vonderweid and colleagues [8] fifteen years later. Ninety-seven Italian NICUs were contacted and asked to participate in an online survey. The medical chiefs or head nurses of 47 NICUs filled in the online questionnaire with a response rate of approximately 48%. The questionnaire was built in order to allow a comparison with the previous survey published in 2003 [8] and explored four main areas of interest. The first section aimed to describe NICU characteristics (e.g. *Number of nurses, number of beds*). The second section explored the role of parents in NICU (e.g., *Are mothers allowed in the NICU?*). The third section focused on environmental care in the NICU (e.g., *Which procedures are*

implemented to regulate lights in the NICU?). The last section was related to the procedure applied to provide infant's care (e.g., *Is Kangaroo Care [KC] proposed to parents? or In providing medical assistance, do nurses take into account infant's sleep/wake rhythm?*). In the current paper, we report data on parents' presence in NICUs and on the distribution of KC and breastfeeding. Moreover, we assess nurses' perception of parents in the NICU as a possible team stress factor. In the present study, 70% of NICUs allowed unrestricted presence of both parents and the percentage raised to 80% considering only mothers' unrestricted access. The results show a significant improvement in parents' participation compared to the De Vonderweid and colleagues' study [8]: parents (23.8%): $\chi^2(1) = 26.04$, $p < .001$; only mothers (29.4%): $\chi^2(1) = 31.72$, $p < .001$. Importantly, relevant differences were found in different geographic areas within the country: while in northern and central Italy 70 to 75% of NICUs offered unrestricted access to both parents, in southern the percentage was only 27% of NICUs. In regard to KC practices, they have spread all over Italy (93% of NICUs), a percentage significantly different from the De Vonderweid's study (67%): $\chi^2(1) = 10.45$, $p = .001$. Similarly, if substantially each NICU foster mothers to breastfeed their infants (98%), only 36% of them allows breastfeeding within the intensive care area. For what concerns staffs' opinions, 61% of those working in NICUs without unrestricted parental access consider parents' access as "insufficient". On the other hand, the presence of parents in NICUs is perceived as a "moderate" or "elevated" source of stress by 38% of the overall sample of responders. In the 2001 survey, 18% of the nurses had considered that the presence of parents "often" or "always" interfered with routine or emergency procedures. Overall, our data suggest an increase of the number NICUs that provide DC procedures in our country. Compared to the previous survey [8], a substantially higher percentage of NICUs provides unrestricted access to parents. Notably, the important role of fathers in supporting both infants and mothers seems to be progressively taken into account. Even more important, the present survey shows that nurses appear to be aware of the importance of DC and provide practices aimed at fostering parent infant bond, especially the KC. On the other hand, a few issues were raised. Geographical differences between northern central and southern areas of Italy remain a specific concern. It is possible that some hospitals struggle

with the resources that are necessary to improve some DC practices. For instance, while the majority of NICUs allow unrestricted parental access, only 7 (15%) provide a bed for parents within the NICUs. Importantly, many NICU professionals have to deal with the additional sources of stress, which originates by the augmented workload due essentially to the parents presence. Similarly, this would imply the need of additional training and supervision of NICU team. The study has some limitations. First, the low response rate does not allow us to describe a complete picture of the DC in Italy. Moreover, the voluntary participation of NICUs tends to decrease the opportunity to consider this sample representative of the all nation, cause of the lack of a geographical homogeneity in the sample recruitment. In conclusion, although these findings suggest an improvement of developmental care-culture in Italy in the last decade, the situation is far from optimal standards. As DC procedures have been associated with both short- and long-term neurodevelopmental outcomes [9], the implementation of DC interventions and family-centered care in our country remains a critical issue for the care of preterm infants and their families.

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LECT 38

FIBEROPTIC PHOTOTHERAPY IN THE ROOMING-IN UNIT: A COMPARISON BETWEEN TERM AND LATE PRETERM INFANTS

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INTRODUCTION

Fiberoptic phototherapy (FPT) allows to lower total serum bilirubin (TSB) levels in healthy neonates maintained in rooming-in with their mothers [1, 2]. Light is delivered through a pad placed directly in contact with the infant skin, offering several advantages: keeping the infant comfortable during treatment, no interruption of exposure during feeding, no need to divide the mother-neonate dyad [1]. The 2004 Cochrane review reported that FPT is less effective than conventional phototherapy in lowering serum bilirubin in term neonates (TN), except when two devices are used simultaneously, when FPT is equally effective. On the other hand, FPT was reported to have the same clinical effectiveness than conventional phototherapy in preterm infants [3]. We hypothesized that new high intensity FPT devices equipped with pads suitable for TN and big enough to be wrapped around the infant body, might be more effective in TN than previous devices.

AIMS

To compare the effectiveness of high intensity blue light FPT equipped with big pads, in term vs healthy late preterm neonates (LPN) with non-hemolytic hyperbilirubinemia, during their hospital stay in the rooming-in unit.

METHODS

We studied 114 healthy neonates submitted to FPT during their hospital stay in rooming-in unit with their mothers. All neonates where submitted to FPT, as a treatment for non-hemolytic hyperbilirubinemia. Study population includes a group of 57 LPN (GA 34-36 weeks) (Group I), born between January 2013 and June 2016 and a group of 57 TN (Group II) born between November 2015 and August 2016, collected to make a comparison between the two groups on the effectiveness of a new FPT device, the BiliSoft LED Phototherapy System (GE Health Care) that

was used for all patients. This high intensity blue light device is equipped with pads big enough to be wrapped around the infant body, thus acting as a double phototherapy. FPT was started according to guidelines of the Italian Society of Neonatology [4]. Accordingly, different TSB starting values were considered for TN and for LPN. FPT effectiveness was evaluated as follows: TSB hourly variation during FPT, treatment duration, percentage of TSB reduction after FPT, TSB maximum rebound, percentage of TSB increase after FPT discontinuation and number of after-discharge checks (**Tab. 1**).

STATISTICAL ANALYSES

Data are reported as mean \pm standard deviation or count and percent according to variables nature (continuous or count/categorical). Study population was divided in two groups according to gestational age (TN vs LPN). The differences between groups were evaluated by the Wilcoxon rank sum test (Mann Whitney U test) or the Student's t-test as appropriate according to non parametric/parametric distribution for the continuous variables; categorical data were analyzed by Fisher's exact test. Correlation between variables has been investigated by Pearson's correlation for continuous variables (r for significant associated variables have been reported). A two

tailed $p < 0.05$ was considered significant. Analyses were performed with Stata/IC 13.

RESULTS

Clinical characteristics of study population and comparative results for FPT effectiveness are shown in the table. LPN started phototherapy earlier than TN and with lower TSB values according to the Italian Society of Neonatology guidelines. Duration of FPT was 50.49 ± 18.37 hours in LPN and 47.58 ± 18.82 in TN (ns) with a 28.86 ± 14.51 percentage TSB reduction after treatment in LPN and 27.64 ± 10.39 in TN (ns). More mature neonates had significantly better response to FPT. In fact, TSB hourly reduction was 0.08 ± 0.06 in LPN and 0.11 ± 0.06 in TN ($p = 0.03$). After stopping FPT, LPN showed tenfold maximum percent rebound than TN group ($p = 0.0007$). Finally, check numbers after discharge were not different between groups. The TBS hourly reduction is significantly correlated with starting value of TBS, age at PT start and PT duration. Birthweight is not related to the effectiveness of phototherapy. Type of delivery, ABO mismatch, infant gender are not associated to TSB hourly reduction (spontaneous delivery vs cesarean section: 0.09 ± 0.06 vs 0.08 ± 0.06 , $p = 0.27$; ABO mismatch vs no mismatch: 0.09 ± 0.06 vs 0.1 ± 0.06 , $p = 0.6$; female vs male: 0.1 ± 0.06 vs

Table 1 (LECT 38). Clinical characteristics of the study population and comparative effectiveness of FPT.

	Late preterm (n = 57)	Term (n = 57)	p
Gestational age (weeks)	35.1 ± 0.8^a	38.6 ± 1.2^a	< 0.0001
Birthweight (g)	$2,657 \pm 481^a$	$3,288 \pm 350^a$	< 0.0001
Gender (male)	26 (45.6%)	31 (54.4%)	0.454
ABO mismatch	8 (14%)	17 (29.8%)	0.069
Rh mismatch	3 (5.3%)	3 (5.3%)	1
Cesarean section	15 (26.3%)	7 (12.3%)	0.095
Apgar score at 5'	9.2 ± 0.7^a	9.7 ± 0.6^a	< 0.0001
SGA	2 (3.5%)	0	0.496
Age at FPT start	48.84 ± 17.56^a	63.33 ± 21.78^a	0.0005
TSB at FPT start	12.62 ± 2.04^a	15.37 ± 2.07^a	< 0.0001
TSB at FPT stop	8.91 ± 2^a	10.97 ± 1.08^a	< 0.0001
FPT duration (h)	50.49 ± 18.37^a	47.58 ± 18.82^a	0.257
TSB reduction at stop of FPT (%)	28.86 ± 14.51^a	27.64 ± 10.39^a	0.608
TSB hourly reduction in FPT	0.08 ± 0.06^a	0.11 ± 0.06^a	0.029
TSB maximum rebound	11.09 ± 2.94^a	12.62 ± 2.5^a	0.0007
TSB increase after FPT discontinuation (%)	13.6 ± 12.7^a	1.28 ± 2.67^a	< 0.0001
Check numbers after discharge	1.91 ± 1.24^a	1.88 ± 1.43^a	0.517

FPT: Fiberoptic phototherapy; TSB: total serum bilirubin.

^aData are expressed as mean \pm SD.

0.09 ± 0.06, p = 0.39). No need for a conventional phototherapy treatment was observed in both groups. FPT was easily managed in the rooming-in unit with good mother compliance. Neither interference with breastfeeding was observed, nor excessive weight loss or dehydration. Infant body temperature was maintained in the normal range in all infants.

DISCUSSION

The 2004 AAP guidelines on management of neonatal jaundice focused on the opportunity “to reduce the incidence of severe hyperbilirubinemia and bilirubin encephalopathy while minimizing the risks of unintended harm such as maternal anxiety, decreased breastfeeding and unnecessary costs or treatment” [5]. FPT makes it possible to treat hyperbilirubinemia keeping the neonates in rooming-in with their mothers, avoiding interference with breastfeeding [1, 2]. However, the 2004 Cochrane review on FPT has raised some doubts about its effectiveness in TN. Since then, new devices have been available for use in TN. Our results, obtained with a new high intensity blue light device and pads that can be wrapped around the infant body, show that FPT is a method of treatment able to lower serum bilirubin in both TN and LPN, while keeping together the mother-neonate dyad and without interference with breastfeeding. Interestingly enough, TN show a statistically significant better performance than LPN in respect with TSB hourly reduction during FPT. LPN started phototherapy earlier than TN and with lower TSB values. Thus, although LPN stopped FPT at lower values than TN, FPT duration was not significantly different, as well as TSB percentage reduction.

CONCLUSIONS

High intensity blue light device equipped with pads big enough to be wrapped around the infant body, thus acting as a double phototherapy, resulted strongly effective in lowering TSB levels in TN as well as in LPN. No switching in conventional phototherapy was needed in both groups of neonates. TN showed a statistically significant better performance than LPN in respect of TSB hourly reduction during FPT. FPT was easily managed in the rooming-in unit with good mother compliance and no interference with breastfeeding, thus minimizing disruption of normal infant care.

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LECT 39

DRUGS AND BREASTFEEDING

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Lactating women can be exposed to medications or other therapeutics, for short or long term, but are often advised to discontinue nursing or therapy because of the risk of possible adverse effects in the infants. Only a very little percentage (1-2%) of products are considered safe in the drug leaflets. Evidences on these topics are lacking or based on animal studies which may not overlap with human features and metabolism. We know that the majority of drugs passes into the milk with several pathways: simple diffusion, carried mediated diffusion, active transport, pinocytosis and reverse pinocytosis, but most of drugs do not concern breastfeeding: not all of them are excreted in clinically significant amount into mother milk and their presence may not represent a problem for the infant. When we counsel a nursing mother about the risk of using a specific drug we have to evaluate three variables: molecule, maternal and infant characteristics. About the chemical properties of a drug we have to consider the following: oral bioavailability, percentage of drug that reaches circulation after oral administration; drug volume of distribution (high volume guarantees a lower plasma concentration with low concentration in milk); high protein bound can reduce drug diffusion. In addition molecules with small size, weak bases, high lipid solubility can pass more easily into maternal milk. The relative infant dose is an important index of the dose received from breast milk (mg/kg/day) and it depends on the mother's dose (mg/kg/day). It is expressed as a percentage and 10% value represents a cut off

but usually values are around 1%. The age of the baby represents the most important characteristic: newborns and even more preemies have a lower liver metabolism with a reduced renal capacity of excretion. These problems become less relevant after two months of life. Furthermore, following *in utero* exposure, the risk of drug accumulation could increase. About maternal and infant metabolism a new promising research field is represented by the ‘omics’ technologies that could create a kind of “metabolic identity card” of the subject. About pharmacogenomics a typical example is codeine metabolism via cytochrome P450 (CYP) 2D6 enzyme: ultrarapid metabolizer mothers should avoid the prolonged use of this drug for the risk of infant severe central nervous system depression. Instead, metabolomics represents the youngest and growing discipline and seems to be a very useful tool in neonatology. We can identify drugs and intermediates contained in human milk, and this kind of analysis may help us in deciding if the drug could be dangerous or represents a hazard for the infant during lactation. Nowadays the Naranjo’s scale is an easy way to value the probability of an adverse drug reaction. Moreover we can use also the Hale’s scale. The Hamletic doubt is: is it safe or is it not safe? Radioactive compounds (technetium and iodine isotopes) are not safe: breastfeeding should be interrupted until the effective dose for the child is less than 1 mSv. For iodine-containing contrast medium, breastfeeding should be interrupted for 24-48 hours. A topic of emerging interest is the use of psychotropic drugs during the postpartum period. The majority of these molecules are not contraindicated and monotherapy is desirable: SSRI, amitriptyline and nortriptyline have a safety profile. On the contrary, more attention is needed for fluoxetine for its long-life, lithium can be safe but a strict monitoring of the baby is necessary, and it could be better avoiding doxepin and nefazodone. Therapy with benzodiazepines must take into consideration the duration and molecules half-life: in few cases high level of diazepam (30 mg/day) was linked to sleeping and feeding disturbances, but single maternal dose does not seem to cause any problems. An antiepileptic therapy can be considered safe with a strict check of infant symptoms. As with all CNS-effective medications, there are no sufficient data on long-term effects on breastfed children. So far there is no serious indication of risk. Pain medication like codeine and morphine should be used with attention, as we have said before, while short-acting agents, such as ibuprofen (Non

Steroid Anti-inflammatory Drugs, NSAIDs) and acetaminophen are safe, although avoiding NSAIDs in breastfeeding infants with ductal-dependent cardiac lesions may be prudent. About antibiotics, we know that breastfed child receive less than 1% of the weight-related therapeutic dose and the only side effect is a temporary thinner stool consistency. What about products to stimulate lactation? The evidence to support these agents called dopamine antagonists (domperidone and metoclopramide) or herbal treatments are lacking and seem to have a limited role in facilitating lactation in comparison to non pharmacologic measures. Finally, breastfeeding is contraindicated in cases of persistent maternal use of heroin, amphetamine, cocaine and alcohol. Practical points: start breastfeeding immediately after delivery (no problems in the first days with colostrum); evaluate every case like a specific case (kind of molecule, dosage, mother’s and child’s clinical situation); consult literature or LactMed database of TOXNET; do a critical check of the infants and their symptoms.

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LECT 40

DRUG-ADDICTION AND SOCIAL UNEASINESS

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Drug-addiction before being a medical issue is a social issue still to be completely understood and explained as remarked by recent studies on the topic. International literature has pointed out that the psycho-social model explains better the origins of drug-addiction; it underlines the role of social uneasiness which includes social and

economical difficulties, marginalization, social contradictions, lack in social abilities, inability to be part of the community and to plan oneself life [1]. Social incertitude and deep restlessness, which characterize the “existential void”, reflect negatively on individual psychology and practical activities. Drug-addiction is addiction to substance and “in-substance”! This means that drug-addicts depend on drugs without filling that void. Drug-addiction is a way through which an individual can be in a relationship with another in a time frame that dissolves as drugs dissolve in the organism; there is the illusion of finding a bond and a refuge in a new social dimension. In the ‘70 these theories were confirmed by authors. In the ‘80 an impressive study conducted in Vancouver surprisingly proved that mice who lived in a safe and happy environment with their kinds weren’t attracted by drug water and avoided it, while mice living alone in a cage and unhappy abused drug water [2]. This example introduces us the issue of social solitude, nurtured by social-networks, smartphone, tablets, etc. where individuals are isolated, leading the way to illicit substances, not just drugs but also alcohol, doping and psychotropic drugs. Isolation and solitude embrace all social levels. What is more shocking about drug addictions is that it is no longer confined to maladjusted individuals or criminal organizations, but it is spread to “normal” families. Subsequently, in recent decades we have witnessed a new trend in drug addiction which has become compatible with an everyday life, far away from the marginalization we knew. This trend is also characterized by more legal and illegal substances taken together, which delays the onset of impairment and the need to ask for help. This trend brings on the integration between drug addiction and a life made of work, family and children. The World Drug Report of 2016 estimates that in 2014 one adult out of 20 between age 15-64 used at least one illicit substance; 247 million individuals used drugs [3]. As for Italy, the last Parliament Annual Report on Addiction (2015) developed by the Department of Drug Prevention reported that in 2013 consume of illicit substances concerned the 20% of young adults (age 15-34); 87% of these consumed only one substance while the 13% two or more. Marijuana and cocaine are the most widespread substances [4]. Within the male population a major consume of psychotropic drugs is observed; what is alarming is that 90% of drug-addicted women are fertile and addiction is known as a pathological condition that interferes with parenting and maternal function.

Drug abuse during pregnancy is associated to lethal or malformative effects on the fetus and to dysfunctional psychological and social patterns in these women [5]. Literature reports a familial, social and environmental impairment for such women throughout childhood and adolescence. These women have difficult access to services for drug-abuse treatment [3, 6]. Families with drug addicted women appear to have structural impairments such as lack of child care and bad parenting. Sometime these women fear to lose custody of their children or fear they have to leave them as a condition for treatment; other can’t afford child care services or treatments itself. Social stigmatization against these women prevents them from recognizing their problem and leaving their home and families to submit themselves to treatment. Worldwide 1 out of 3 drug addict is a woman and yet only 1 out of 5 individual in treatment is a woman. The less information we have on drug-addicted women the more there is a lack of tailored and evidence-based treatments for women, especially in poor countries [3]. Drug abuse and addiction are seen as individual features that affect parents’ ability to take care of the child. Furthermore, parents’ lifestyles and maternal features affect parenting and bonding with the child, which impairs its cognitive, emotional and relational development [5]. Harmful outcomes on children due to drug abuse are well known in literature. Newborns are featured with biological vulnerabilities that can hardly be recovered in an adverse environment; such vulnerabilities can be worsen by parents’ drug-related behaviors like dysfunctional parenting, abstinence, compulsive search for drugs, violence, poverty, unstable housing, incarceration and psychiatric comorbidity for depression, affective and personality disorders. Finally, the role of social, psychological and local resources is clear in building individuals’ wellbeing and the role of specialized facilities to set networks for individuals’ protection against the onset of addictions, particularly drug assumption.

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LECT 41

FOLLOW-UP OF THE INFECTED NEONATE

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Many microorganisms can infect the fetus/newborn during fetal life (prenatally), around birth (perinatally) or in the neonatal period (postnatally). These infections are generally comprised into the TORCH acronym (cytomegalovirus [CMV], *T. gondii*, *T. pallidum*, varicella, rubella, human immunodeficiency virus [HIV], hepatitis B virus [HBV], hepatitis C virus [HCV], herpes simplex, parvovirus B19) but early and late onset neonatal sepsis should be included between neonatal infections deserving an accurate follow-up. All these infections globally represent, particularly in low-middle income countries, a major cause of neonatal mortality, morbidity and impaired long-term neurodevelopmental outcome [1]. The incidence of TORCH infections in newborns is closely linked to the prevalence of these diseases in reproductive-age women in that it may affect the risk of vertical transmission in a directly (i.e. HIV, Syphilis, HBV, and HCV) or inversely proportional (i.e. Toxoplasmosis, Rubella, Varicella, Parvovirus) way. Interestingly, CMV may determine both primary and non-primary infections during pregnancy and the burden of each type of infection will depend on CMV seroprevalence during pregnancy. In this regard, migratory flows represent an important issue to be considered. Rubella, due to vaccination campaigns, tends to disappear (2015 has been the first year in which no case of congenital rubella has been reported in Italy) but a new microorganism with similar teratogenic properties, the Zika virus, is currently in the spotlight; whether and to what extent this infection will spread in our

latitudes will depend mainly on virus circulation, global warming, spreading of animal vectors, and viral genetic mutations possibly increasing the fitting of the virus-vector dyad [2]. Nonetheless Zika virus, starting right now, must be included in the differential diagnosis of infant's diseases occurring with microcephaly and/or brain calcifications. Pregnancy represents an extraordinary opportunity to perform public health policies and no mother and infant should miss the opportunity to be screened for TORCH infections. The fetus/newborn may greatly benefit from the identification of an infected mother in different ways:

1. Treatment during pregnancy may prevent vertical transmission – this has been clearly demonstrated for HIV, Syphilis, Toxoplasmosis and, recently, HBV maternal infections [3]. Keeping with this, national guidelines on physiologic pregnancy should rapidly take into account the new acquisitions and be modified accordingly.
2. Maternal treatment may cure infected fetuses – pyrimethamine and sulfadiazine cross the placenta and effectively cure fetuses infected with toxoplasmosis; a phase II trial has recently demonstrated that high-dosage valacyclovir, when given in pregnancy, improves the outcome of moderately symptomatic CMV infected fetuses [4].
3. Neonatal prophylaxis – sons of HIV positive mothers must undergo a 6 weeks zidovudine prophylaxis to prevent vertical transmission; HBV vaccine and immunoglobulin administered soon after birth currently represent the cornerstone in the prevention of HBV vertical transmission.
4. Identification at birth of congenitally infected asymptomatic newborns – this definitely is the most frequent eventuality for the neonatologists; as an example, virtually all infants congenitally infected with hepatitis viruses and roughly 85% of newborns congenitally infected with CMV and toxoplasma are asymptomatic at birth. Nonetheless, these babies need therapy and/or a prolonged follow-up and diagnosis of infection would be missed in absence of prenatal screening. Although prenatal diagnosis performed on amniotic fluid, by means of culture or NAT (Nucleic Acid Testing), may in some cases diagnose fetal infection (i.e. CMV and toxoplasmosis), neonatologists frequently have to face symptomatic or asymptomatic possibly infected infants. Ruling in/out neonatal TORCH

infections is a time- and resources-consuming activity; in fact, due to frequent uncertainty about infection (IgM absence at birth never exclude a neonatal infection and a single NAT is seldom sufficient to rule it out), a thorough evaluation of the infant is always requested at birth to investigate for possible damages due to infection. Moreover, repeated blood sampling along several months (using NAT and/or evaluating the kinetics of the Immunoglobulin G) is often performed to definitively rule infection in/out and every effort has to be made in order not to lose these babies during follow-up. The sequelae of a TORCH infection may occur at birth, during infancy, or years later. These infections may virtually affect every organ system and central nervous system involvement affecting neurodevelopmental outcome is possible; a several year-long follow-up is then mandatory. While infants with HBV, HCV, and HIV infections are generally referred to pediatric infectious diseases experts, neonatologists may decide to take charge of the follow-up of some infected babies dealing with the timescale of a complex multi-specialties follow-up; Italian multi-society guidelines concerning the management of congenital CMV, Toxoplasmosis and Syphilis infections are currently available on the website of the Italian Society of Neonatology [5].

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LECT 42

WHAT COMES AFTER A NEWBORN HEARING SCREENING PROGRAM? ACHIEVEMENTS AND CHALLENGES

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INTRODUCTION

Hearing loss is the most prevalent developmental abnormality present at birth with an incidence calculated in 1-3 per 1,000 live births and represents a significant public health issue. The American Academy of Pediatrics (AAP) endorses newborn hearing screening in order to reach early detection and intervention for infants with hearing loss. Our region enacted legislation requiring all birthing hospitals to conduct hearing screening since 1st January 2012. In accordance with the Joint Committee on Infant Hearing (JCIH) Year 2007 Position Statement all the infants should undergo screening at no later than 1 month of age and infants with confirmed hearing loss should receive appropriate treatment at not later than 6 months. Separate protocols are recommended for NICU and well infant nurseries. The same legislation introduced a multidisciplinary team, named TADU (*Tavolo Aziendale Disabilit  Uditiva*) with the objective to predispose efficient integrated care pathways for children. Building the capacity to provide newborn hearing screening and follow-up services implies a great organizing effort. The aim of this study was monitoring the cases of children with hearing loss in charge to our Youth and Childhood Neuropsychiatry Service (NPIA) in order to better understand local needs and to reorganize, if necessary, intervention services.

METHODS

More than 6,500 babies are born in Modena county every year in 5 birthing hospitals, and around 3,000 are born in the University Hospital where a NICU is present. A common database has been created and each birth hospital sends its data to the coordinative centre in Primary Care Department. Families and community pediatricians have been involved in the building of the program in accordance with the principle of carrying out the screening under the best auspices. Modena county has a population of around 688,000 inhabitants, of which 15% is under 14 years aged. The screening is carried out by means of transient stimulus evoked otoacoustic emissions (TEOAE). For healthy babies a two-stage protocol is used: the first screening stage is carried out on the second day after birth followed by rescreening before discharge if a pass response is not obtained in both ears; a second stage follow-up screening is carried out within three weeks in case of failure and a complete audiological evaluation is

performed in case of a persistent failure response. TEOAE test is administrated by dedicated nurses, obstetricians or audiology technicians, depending on the organization in each birth hospital. Newborns presenting audiological risk factors are screened by both TEOAE and ABR at first stage, according to the JCIH 2007 Position Statement. All the newborn families received the appointment for ABR at the discharge from hospital. Modena screening program includes an audiological follow-up at one year of age for the children considered at risk for postnatal hearing impairment or delayed language development. The update of our database regarding children and teenagers with hearing disorders who are followed by NPIA of local health service, has been the starting point for this study. The research focused on patients with a diagnosis of hearing impairment (classified according IDC.10 system) in charge at the service.

RESULTS

In the year 2015, 6,246 children were born in the 5 birthing hospitals of the county and all underwent hearing screening. 3,055 underwent the TEOAE screening test in University Hospital of Modena whereas the number of ABR testing including children coming from the whole county was 372. 12 children resulted to be affected by hearing loss. Data collected from NPIA service, since 1989 until 31st December 2015, regarded 281 patients Children under 18 years were 232, 73 in preschool age, 91 in school age. Males were 60%. The distribution according to the year of take in charge in the service shows that the number of patients is growing constantly. In 23% of cases hearing loss was profound, in 26% of cases severe. 10 children were born in 2015. In 57 cases congenital malformations were present.

DISCUSSION

Data collected show the efficacy of both the Universal hearing screening and the early intervention program in our county. A newborn hearing screening protocol without an appropriate intervention service for infants with hearing loss is not functional to the goal to maximize linguistic competence as children need prompt access to quality intervention services. Creating an active collaboration between audiologist\ENT specialists, family, pediatricians and births hospitals is basic as problems in continuity and in communication between examiners and the family can condition the results.

CONCLUSIONS

The way to successful achievement of early detection and treatment of bilateral permanent

congenital hearing impairment is not simple. Data storage system is crucial for the monitoring of children hearing impairment, not only in order to develop rehabilitation programs but also for a prediction of health needs that underlies every regional planning. A flexible and near to family organization is necessary to assure an early and correct access to services to provide continuity of care and high quality cure.

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LECT 43

ACUTE KIDNEY INJURY IN NEWBORNS

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Acute kidney injury (AKI) is defined as a rapid deterioration of renal function resulting in retention of nitrogenous wastes and other biochemical disorders [1]. In general, nephrogenesis begins at the fifth week of gestation and continues until 34 to 36 weeks when the number of nephrons rises to 1.6-2.4 million. There are significant changes in postnatal renal blood flow: at birth kidneys receive 2.5% to 4.0% of the cardiac output, at 24 hours of life 6%, at 1 week 10%, and finally at 6 weeks of age around 15% to 18% [2]. These changes in renal blood flow lead to an increase in renal perfusion pressure, an increment in systemic arteriolar resistance, and a fall in renal vascular resistance [3]. Hormones such as angiotensin II and prostaglandins also have a part in this process. To distinguish AKI on the basis of pathophysiology, it can be classified in prerenal, intrinsic, and postrenal. Assessment of gestational age, maternal nephrotoxic medications, Apgar score at birth, and postnatal events (nephrotoxic medications, hypotension) are fundamental details of clinical history to precisely evaluate a newborn affected with AKI [4, 5]. Furthermore, it is necessary to well overview of newborn's volume status with assessment of serum electrolytes, fluid balance, and

body weight. Early recognition of AKI risk factors may reduce its occurrence [6]. In term newborn (not always in premature infants) detection of fractional sodium excretion can help to differentiate prerenal AKI (hypovolemia, dehydration, hypoxia) from intrinsic forms (e.g. acute tubular necrosis). In preterm infants the main reported causes of AKI are prerenal (85%). Prolonged prerenal injury can result in intrinsic AKI due to hypoxic/ischemic acute tubular necrosis [4]. Premature infants are at higher risk for AKI due to prenatal fetal distress and exposure to multiple risk factors such as infections, placental insufficiency, drug medications and intrauterine growth retardation. Some causes of kidney hypoperfusion are an hemodynamic significant PDA (with left to right shunt) and use of pharmacological therapy with nonsteroidal anti-inflammatory drugs [7]. In preterm infants, the 50% of all acute renal failures has been linked to postnatal drugs exposure for treatment of sepsis (especially cephalosporins) [1]. The incidence of AKI in newborns is accounted for 8-24% [2] rising up to 71%, in newborns with congenital heart disease or congenital diaphragmatic hernia [8, 9]. In preterm infants the incidence varies according to gestational age and it has been reported to be 30.3% in EBLW [10] with a mortality rate from 33 to 78% [11]. Before the advent of therapeutic hypothermia, AKI affected 47-72% neonates with perinatal asphyxia. A more recent studies, based on the Acute Kidney Injury Network (AKIN) criteria, reported an incidence rate of 9.1% in those who have moderate asphyxia, of 56% in severe asphyxia [12] and of 38% in neonates treated with therapeutic hypothermia [13]. Newborns who have suffered from AKI are at risk for late development of kidney disease also several years after the primary insult [14]. Often, in the premature population, AKI is unrecognized or underestimated [5]. Indeed, the two most commonly used markers to identify AKI, serum creatinine (SCr) > 1.5 mg/dl and associated oliguria (urine output < 0.5 ml/kg per hour), could not be sensitive markers [1]. In fact, at birth serum creatinine reflects maternal levels and decline at varying rates over days to weeks, depending on gestational age [11]. Because newborns usually have non oliguric renal failure (in particular VLBW), an AKI classification has been proposed that does not include urine output [14]. Once diagnosis of AKI has been made, it is important to monitor and prevent possible future complications. Measuring drug levels and avoiding nephrotoxic exposures should be routinely performed, as well

as recording fluid intake, serum electrolytes, and weight loss may guarantee clinical stabilization. According to some authors, adenosine receptor antagonists (theophylline) may prevent AKI in neonates with perinatal asphyxia by inhibiting the adenosine-induced vasoconstriction [7]. Also dopaminergic agonists (dopamine and fenoldopam) seem to be useful to prevent renal failure [7]. Diuretics are frequently used in attempts to maintain urine output, but different studies in critically ill patient have not demonstrated a beneficial effect of diuretics on newborn outcome [7]. In the case of medical management failure, renal supportive therapy is considered a last chance to rescue [15]. The use of hemodialysis and hemofiltration have been replaced by peritoneal dialysis (PD). The latter is not routinely performed in preterm infants due to the size and shape of the peritoneal catheters and abdominal wall thickness, lack of machines designed for neonates and technical difficulties associated with access placement [16]. Moreover, regarding the high rate of mortality using PD, practitioners may defer that last opportunity in favor of diuretic therapy and nutritional restriction. PD should be started in patients with fluid overload (> 15% fluid balance) hyperkalemia (> 7 mEq/l) or intractable acidosis [1]. Clinical symptoms of uremia (e.g. effect of neurotoxicity), persistent oliguria or anuria (despite adequate hydration) and persistent and symptomatic hyponatremia could be other factors that influence starting of PD [16]. The major complications of PD are catheter leakage or obstruction, infective complications (peritonitis), bleeding or intestinal perforation. Limited available literature documenting the use of PD in preterm infants describes uniformly high rates of technical complications (25-60%) and mortality (> 50%) [15]. When PD is technically difficult because of abdominal wall defects, intestinal problems, or high ultrafiltration needs, continuous renal replacement therapy (CRRT) can be chosen.

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LECT 44

PRESSURE ULCERS AND SKIN TEARS PREVENTION IN A NICU WARD, A NURSING PROTOCOL FOR AN EARLY IDENTIFICATION AND AN EFFICACIOUS PREVENTION

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BACKGROUND

In the last years pressure ulcers have become a well-known issue in the adult patients and skin care has improved. On the contrary, this problem still remains underestimated in the pediatric population, especially in neonates, although it is a very important topic. The incidence of pressure ulcers is about 23% in Neonatal Intensive Care Units (NICUs),

and can develop within the first 48 hours from admission [1]. However, not all pressure ulcers that occur in a NICU are documented as the problem is underestimated. According to the recently changed definition of the National Pressure Ulcer Advisory Panel (NPUAP), a pressure ulcer, now called pressure injury, “is localized damage to the skin and/or underlying soft tissue usually over a bony prominence or related to a medical or other device. The injury can present as intact skin or an open ulcer and may be painful. The injury occurs as a result of intense and/or prolonged pressure or pressure in combination with shear” [2, 3]. As shown by a study (sample composed of children aged from 21 days to 8 years), the most common area for pressure injuries is the head (41%), especially the occiput. Neonates at higher risk are those with reduced mobility, that is secondary to the following factors: fixed or limited postures (as it happens for surgical neonates, also because of sedation and use of neuromuscular-blocking drugs), extreme prematurity, therapeutic procedures (such as therapeutic hypothermia, plaster cast, skin traction) and cognitive or mobility deficit. An additional important risk factor is the presence of devices, especially if multiple or in the same area for a long period. Other risk factors include the following: gestational age less than 32 weeks and weight less than 1,000-1,500 g (due to the immaturity of the integumentary system), dehydration, poor nutrition, edema and all those factors that negatively influence tissue oxygenation and perfusion (cardiovascular disease, glycemic instability and use of vasopressors). Another skin injury that occurs in a NICU is the skin tear that is “a wound caused by shear, friction, and/or blunt force resulting in separation of skin layers [...]” [4]. Skin tears risk factors are the following: presence of bruise, long-term treatment with corticosteroids, skin cleansers, cardiovascular and pulmonary diseases, dehydration, poor nutrition, previous skin tears (because that area, even if already healed, has a reduced traction resistance), gestational age (because of the lower cohesion between epidermis and derma); this happens especially in the preterm infants, as the dermo-epidermal junction and the corneous layer are scarcely developed. When a skin tear occurs, its healing can be negatively influenced by protein-caloric malnutrition, hypotension, edema, infections and patient instability.

METHODS

The importance of this subject, and the lack of homogeneity in skin care management in our NICU, led us create a working group composed of nurses,

in order to ensure uniformity in wounds prevention and management. The group followed six phases:

- a. formation of the group and identification of its targets: evidence-based prevention and management of pressure ulcers (and other skin injuries); improving nursing efficacy and efficiency in the care of infants with reduced mobility, who are at a major risk of pressure injuries; developing continuity of care and making the progression of the wound (onset, evolution and healing) more traceable to allow the study of incidence, risk factors and treatments efficacy;
- b. analysis of the strengths and critical aspects of our ward current skin care;
- c. bibliographic research through national and international databases (especially Medline and Embase), international guidelines and wound care and neonatal books [5-18];
- d. creation of protocols and related tools;
- e. validation of one protocol;
- f. revision, planned for September 2017.

The efficacy of the protocols will be monitored by using a tool created by the group: “NICU Wounds Monitoring Sheet”.

RESULTS

A nursing protocol for the prevention of wounds (P/LCN) was created; a nursing protocol for the management of wounds (G/LCN) is still under construction. These protocols include the use of Pressure Ulcer Risk Assessment Tools like NSRAS, chosen by the group to assess the risk in patients under 28 days, and the Glamorgan Scale, chosen for patients over 28 days, and also a Neonatal Skin Condition Score (NSCS) that facilitates and makes evaluation of the skin uniform during the daily head-to-toe skin inspection. It was also necessary to create other tools, as the “Wounds Chart”, that allows to have the patient “skin story” from admission to discharge in one singular sheet, including the reference to the protected discharge, when needed, and the “Pressure Ulcers Prevention Program at Home”, a sheet with a personalized program that helps parents of infants at moderate/high risk preventing pressure ulcers. This plan needs then to be reevaluated by the domiciliary nurse. G/LCN, conversely, includes tools as “Wound Evaluation Sheet – First Evaluation” and “Wound Evaluation Sheet – Reevaluation”. Moreover, the use of these protocols has involved pressure ulcer prevention and treatment educational program to all nurses of our NICU ward, to show how use the tools, and how to evaluate and act in a uniform way. The aim of this

program is also to increase motivation to make the problem less underestimated.

CONCLUSIONS

Pressure injuries, skin tears and other neonatal skin injuries can be cause of pain, local and systemic infection and secondary scarring. Pressure injuries can also cause alopecia in the wound area. Moreover, they can cause prolonged hospital stay and increased management costs. But pressure injuries and skin tears can – and must – be prevented, as the maintenance of skin integrity is one of the clinical indicators of nursing care quality and, as highlighted by *The Nurses’ Deontological Code* (2009) [5], the nurse, as the healthcare professional in charge of nursing care, protect health also through prevention.

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LECT 45

THE SINGLE FAMILY ROOM: THE EXPERIENCE OF MONZA

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The Neonatal Intensive Care Unit (NICU) of Monza during its history has experienced a gradual but steady opening to the parents of hospitalized babies. In 2010, the prospect of a new facility dedicated to the areas of intensive and intermediate neonatal care represented a valuable opportunity for skills upgrading. Thus, a delegation of leaders of the structure reviewed the most current literature and visited some of the NICUs that were experimenting new design models. Such study helped the staff (who has meanwhile seen the design changes of its units from small areas with 4-6 beds to two large areas with 12 beds) in understanding the needs of patients, parents and operators and focusing the theoretical and practical aspects of the impact of the environment. A medical-nursing "care" group was therefore created, who identifies the "Family Centered Care" as a role model of the health care process. At the same time, another new group

called "NICU-Design" identifies in the "Evidence Based Health Design" (EBHD) the reference model for the choices about the environmental structure. The two models can be perfectly integrated with each other and are congruent. The EBHD is an adaptation of architecture and engineering to the needs of the evidence-based medicine. In this model the environmental configuration and the design components are effectively treated as care tools. The theoretical foundations of this approach are three: 1) the environmental congruence, i.e. the need to modulate the environmental stimuli on the basis of the resources and expertise of the subject that is in the environment, by acting on materials, sounds and lighting; 2) the positive distractions which are structural or decorative elements that help to ward off unpleasant thoughts and to relieve stress. Elements derived from nature and art included in the furniture can achieve this goal, as well as special areas for relaxation and leisure; 3) the participation of all the components to the project in order to meet the needs of everyone and build a design that reflects not only the needs, but also the vision of babies, families and staff. In fact all EBHD theoretical foundations are addressed to the three actors of care: patients, family and staff. In 2012 the results of this preliminary work led to the identification of the "single family room" (SFR) as the structural model that best corresponds to the respect for the family-centered care with the efficacy reported in different experiences. In fact, a department consisting of single rooms, where babies and mothers can stay together 24 hours a day, has a positive impact on bonding; it also facilitates the infection control and reduces days of respiratory assistance as well as the number of procedures, the neurological symptoms, stress and pain; it promotes nutrition and weight gain, too. It has a positive impact on parents who feel more involved in the baby's care, have their privacy and can feel the room as their own, especially if they have the possibility to customize it; the final effect is that parents stay longer next to the child and feel they have more attention from the staff. The addition of areas dedicated to parents enables them to meet each other promoting self-help mechanisms. The SFR model has a positive impact also on the staff: it improves the relationship with the families, reduces stress and increases the perception of working well with the patient, provided that the staff possesses all the facilities that foster communication and has places dedicated to rest and "decompression". Since 2014 a multidisciplinary task force made up

of doctors, nurses, parents, architects and engineers, has been reworking the design already drafted by the contractor and has proposed an intensive care unit in which the rooms are designed for a single patient (maximum two in case of twins) with areas specifically decorated for the baby, the family and the staff. In the project monitoring and service areas, rest areas for families and staff are also contemplated and arranged. The staff has reacted with enthusiasm to the innovative project, but has shown anxiety mainly related to isolation and the need for reorganization of the nursing work. This implies the definition of objectives (organizational, clinical, management and for safety) and the establishment and coordination of working groups with the involvement of all the components that live and work within the structure.

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LECT 46

NON-STOP ASSISTANCE IN NEONATAL FIELD: PROPOSAL FOR A MANAGEMENT MODEL

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INTRODUCTION

The Complex Structures of Neonatal Nursery at the Obstetric Gynecological Hospital “St. Anna” in the AOU, Science and Health City of Turin, offer comprehensive and highly specialized medical assistance. Preterm and pathological infants may present complications (medium and long-term)

associated with prematurity and/or concomitant diseases at birth. With regard to these complications, if they are not solved during the period of hospitalization, they require a discharge planning in order to provide proper non-stop assistance and avoid extra days in hospital. The Non-stop Assistance Service within St. Anna hospital is the executive operations center with the coordinating role of the relationship between hospital and territory, in line with the organizational model dictated by DGR27/2012, which includes, among its key points, the institution and the activation of the Hospital Nucleus of non-stop assistance NOCC (Nucleus Hospital Continuity of Care). Since the BRASS sheet is not used for this population’s age, it was necessary to build a tool that allows identifying infants at risk of difficult discharge. Its early identification has the expressed goal of being able to promptly activate the NOCC, all the necessary resources in the area, and facilitate the return to home of the newborn and his family.

PROJECT OBJECTIVE

The objective of this project was the predisposition of an information tool facilitating the identification of critical issues of the pathological newborn. The realization of such shared tool represents an improvement in the quality of care because the rating scales and assistance indexes encourage an objective reading of the care and comparable phenomena. The goal is to achieve homogeneous qualitative and quantitative assessment of the assistance and promote the communication and information exchange among different disciplines.

METHODS

The predisposition of the tool came from a request made by Non-stop Assistance authorities and by the entire neonatal nursery. Such purposes gave birth to a collaboration with the Coordinator of Non-stop Assistance with whom all activities and a proper path to follow were outlined. The first stage consisted of a review of the literature, focused to identify: complications at birth and clinical and/or socio-medical elements, dependent and related to the duration of hospitalization, which represents the conceptual structure for the realization of this tool. Then, we proceeded to prepare the medical sheet; A first test was conducted in order to verify the applicability of elements drawn from literature to Italian reality. In this first test (lasting three months) infants born with gestational age less than 33 weeks of life were identified and subjected to monitoring, from the time of acceptance until discharge. The monitoring occurred in three moments of stay:

on the first day of hospitalization, the first week and at 28 days of life. The first tests showed that observations were concentrating on the first month of life, at the expense of the following months with the difficulty of assessing the clinical variations. The project team to make changes in content and format has revised the sheet after this first phase. A further period of testing was subsequently identified to verify the appropriateness of the sheet and its adaptability to context. In this occasion, on the basis of the first phase of testing, it was necessary to introduce some criteria necessary to select a more specific type of newborns. The new identified criteria outlined a subset of infants to be enrolled with the NOCC sheet: gestational age less than 30 weeks of life, concurrent pathologies at birth, underwent treatment and hypothermic newborns bearers of medical/surgical devices. The monitoring points have been modified identifying the first after seven days of life and the second one to the thirty-seventh week accomplished gestational age. It is only after the second observation that we proceed to the written communication via the computer system company to NOCC. The third section allows recording the presence of care needs that require activation of the territory or the formation of the caregiver; in this case the monitoring will be continued with a weekly basis. The sheet has been tested on 60 cases (from October 2015 to May 2016) to assess its applicability.

RESULTS

The “Criticality Identification Sheet for Pathologic Newborn” has been created. This document is made up of three sections, distributed on two pages. In the first section it provides demographic information of the infant, the family anamnesis, neonatal complications and care needs. The second section is dedicated to elements that provide information on the clinical stability or instability of the newborn: respiration, nutrition and elimination. These elements, which have emerged from the literature research, can determine a qualitative and quantitative assessment, regarding the possible discharge of the newborn. These elements have been organized in two tables, and provide a complete picture of the first 28 days until the completion of the thirty-second week, when, according to the literature, the baby develops the most extended numbers of his skills. This period allows to collect clinical data and to extract information in order to plan the discharge path.

CONCLUSIONS

The medical sheet, shared with the team of the different structures, received a favorable assessment

by professionals and managers of health services; for this reason it will be applied in neonatology.

LECT 47

NURSING OF SUBCUTANEOUSLY TUNNELED EXTERNAL VENTRICULAR DRAINAGE IN INFANTS WITH POST-HEMORRHAGIC HYDROCEPHALUS

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INTRODUCTION

Intraventricular hemorrhage in preterm infants is one of the major causes of neurological morbidity and mortality during the neonatal period. The overall incidence of intraventricular hemorrhage in very low birth weight infants is about 20% with an increased incidence of adverse outcomes in extremely low birth weight infants. Twenty-five percent of infants affected by intraventricular hemorrhage may develop a posthemorrhagic ventricular dilatation, which requires implantation of a permanent ventricular peritoneal shunt. A ventricular peritoneal shunt can be positioned only after the cerebrospinal fluid has cleaned up from the blood to avoid its obstruction. Furthermore, the size of the valves makes difficult their use in very low birth weight infant so the typical surgical procedure for implantation of the drainage must be changed. The implantation of a subcutaneously tunneled external ventricular drainage is a non-invasive temporary drainage system that allows waiting the time the neonate reaches the conditions for permanent ventricular peritoneal shunt placement. Catheter placement can be carried out by the neurosurgeon in the neonatal intensive care unit (NICU) in collaboration with its medical and nursing staff. This technique represents a new effective neurosurgical opportunity with clear benefits in terms of morbidity and mortality, carried out at the bedside, safe and with low cost, which requires specific nursing care that can be done in collaboration with parents.

NURSING CARE

The nursing care is divided into three phases: pre-, peri- and post-operative. In the pre-operative phase a NICU's area is temporarily and exclusively dedicated to the procedure. A nurse is dedicated to the infant for all the duration of the procedure (about 60 minutes). The infant is positioned in a hybrid incubator that can easily be “opened” to

perform surgery, equipped with radiant lamp that allows at the same time to provide heat and control the temperature of the newborn, thus minimizing the stress. The nurses check the list of the equipment and devices to be used during the procedure. During the perioperative phase the infant is intubated and sedated; the trichotomy of the scalp is done if there are hair and the neurosurgeon requires it. The skin of the head is disinfected as for a normal surgical asepsis. The neurosurgeon places the external ventricular drainage adapting a feeding tube (Polyurethane 5 Fr) because there aren't commercially available devices suitable for such small patients. The post-operative phase, after the implantation of the drainage, includes precautions that should be observed daily during infant care. Inside the incubator are used sterile linens; this is reduce risk of infection and is a "visual alert" for the medical and nursing staff because the sterile linens have a different color from the normal linens use daily for the infant. The tip of external ventricular drainage is closed in a sterile pouch to reduce the risk of infections and the risk of erroneous use of the external ventricular drainage as a feeding tube. All the infant's devices are single-patient like the meter for head circumference measurement and cranial ultrasound probe gel; the cranial ultrasound probe is disinfected with towel chlorhexidine 2% before and after use on the infant. Sterile gloves without powder on must be used for all maneuvers on the infant, except for the diaper change. Particular attention concern the moment of opening of the system for the drainage of cerebrospinal fluid. It must be performed with sterile technique by two operators (a doctor and a nurse); this drainage is performed daily or several times a day and usually cerebrospinal fluid samples are collected for chemical-physical analysis. The dressing of the drainage entry point is an extremely critical procedure because of the risk of infection and the risk of dislocation of the drainage; for this reason it should be done just when visibly dirty or bungled using a sterile technique by two operators.

CONCLUSIONS

The implantation of subcutaneously tunneled external ventricular drainage is a new technique; for this reason no guidelines are available in literature. This technique offers many advantages for both the infant and operators who assist him; the major strengths of this procedure are:

- possibility to be performed at patient's bedside with reduction of risks related to the transport of a critical infant to another hospital or to the operating room;

- employment of medical and nursing staff of NICUs in collaboration with the neurosurgeon;
- use of easy available and low cost material for drainage implantation;
- possibility of long stay of the drainage which gives time the cerebrospinal fluid to clean up;
- increased comfort for the baby who can be dressed and moved freely (kangaroo mother care could be done if the conditions of the infant permit it);
- easy involvement of parents in their child daily care;
- not painful cerebrospinal fluid drainage, which does not require sedation unless the non-pharmacological techniques (holding, sucking the pacifier with sucrose or breast milk drops).

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LECT 48

MELATONIN IN THE PAINFUL PROCEDURES OF THE NEWBORN

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INTRODUCTION

Scientific evidences suggested that acute and repeated pain causes hormonal alterations in newborns (N), in particular in preterm newborns (PN), with potential short- and long-term detrimental effects, but also in term newborns (TN). Many studies have observed the efficacy of non-pharmacological techniques in neonatal analgesia. The aim of the study was to evaluate N after melatonin (MLT) or 33% glucose solution (GLC) administration.

METHODS

Seventy-eight consecutive newborns (at term [TN] and PN) were enrolled from January to May 2016 and randomly double-blind assigned to receive MLT 1 mg (4 drops) or GLC 4 drops by pacifier, 3 minutes before capillary draw from heel for neonatal screening, performed by an automatic spring retractable lancet (Group A). A second group of 52 N (Group B) received MLT 1 mg 15 minutes before capillary draw. N, during capillary draw, were evaluated by dedicated pain scales (Neonatal Infant Pain Scale, NIPS; Premature Infant Pain Profile, PIPP; Douleur Aiguë du Nouveau-né, DAN).

RESULTS

In Group A, 36 babies were randomized to MLT (12 TN, 24 PN) and 42 to GLC (22 TN, 20 PN). Among MLT newborns, pain score was present in 12 TN (100%) and in 3 PN (12.5%); among GLC newborns, pain score was present in 10 TN (45%) and no one PN. Mean pain threshold evaluated by NIPS was 7/5 in TN treated by MLT and 6.2/5 in TN treated by GLC. Mean pain threshold evaluated by PIPP was 4.4/12 in PN treated by MLT and 5.3/12 in PN treated by GLC. In Group B, 26 TN and 26 PN were enrolled: pain was present in 8 TN (31%) and in 2 PN (8%).

CONCLUSIONS

In this pilot study, performed on a low number of newborns, GLC was more effective than MLT to control N, in particular TN; given that below threshold among babies in which MLT and GLC was effective is comparable, it might be useful to consider a longer induction time for MLT. When MLT had been administered 15 minutes before capillary draw, its efficacy was comparable to GLC, probably due to different mechanisms of pain inhibition.

LECT 49

HIGH-FLOW AND LOW-FLOW RESPIRATORY SUPPORT: NURSE MANAGEMENT OF THE DEVICES

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Oxygen therapy indicates the administration of oxygen with a fraction of oxygen (FiO₂) higher than 0.21%. The management of devices for oxygen administration has to take into account

both the delivery instruments for the medical gas supply and their monitoring systems. The use of oxygen therapy has progressively increased over the past decades, mainly due to the spreading of the devices in critical and non-critical units, to the ease of their maintenance, and also to the advantages deriving from at-home use of oxygen in order to reduce prolonged hospitalization [1]. This has determined a growing requirement for training of caregivers, for both in-hospital use and for at-home delivery. The correct and appropriate use of oxygen therapy, as for every drug, increases its efficacy, reduce side effects and maximize the global benefits for patient's health, reducing social costs and workload for dedicated personnel and families. The technological advancement of the new devices and the multiple interfaces they can be connected to, require the users to have a perfect knowledge of their function, benefits and potential risks. Respiratory support for high-flow and low-flow oxygen therapy requires devices and interfaces (mask or nasal-cannula) that have to warranty proper heated humidification allowing the adequate airways clearance and reducing mucous damages and the consequent increase of work of breathing and secondary infections. The tools that can be used have to allow an adequate monitoring of the amount of oxygen and flow administered to the patient and also the levels of heating and humidification of gas mixture. Low-flow respiratory support, that in neonatology and pediatric indicates a flow lower than 2 L/min, adopts interfaces with variable performance and the FiO₂ cannot be properly estimated, since the administered flow includes room-air and oxygen and is strictly dependent on patients' respiratory system. The heating and humidification of the oxygen are not necessary in presence of an adequately humidified environment. High-flow respiratory support requires the use of an heated and humidified mixture of air and oxygen with a flow higher the inspiratory peak flow of the patient (more than 2 L/min, up to 10 L/min) with several benefits including: reduction of ventilation-perfusion mismatch trough the generation of a positive end-expiratory airway pressure, an improved mucociliary clearance, a reduced death space due to the CO₂ wash out and the administration of a well defined fraction of oxygen [2]. The availability of a proper protocol for the use of the devices for low-flow and high-flow respiratory support improves their management from the staff of neonatal and pediatric units. Here

we propose a table, designed as a tool to improve the use of devices, interfaces and monitoring systems in neonatal and pediatric units in order to provide the personnel with a quick checklist for the set up of the instruments they are going to use. This tool may result extremely helpful in settings that require a long training for the dedicated personnel (both nurses and physicians) as the academic institutions or teaching hospitals where the turn over of caregivers is high as well as the need for a quick and adequate management of several challenging situations. The table has been designed including three main areas: 1) the device

for oxygen administration; 2) the interface; 3) the monitoring. Details are reported in **Tab. 1**. All the three areas are evaluated for the administration of both high- and low-flow respiratory support with the specific troubleshooting. This visual tool is mainly designed for nurses who are in charge of the patient with a non-invasive ventilator support.

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Table 1 (LECT 49). Devices and interfaces for oxygen administration.

	High flow	Troubleshooting	Low flow	Troubleshooting
Devices for oxygen administration				
Source of air and oxygen (column, ceiling drop or wall cluster)		Check for the connection to gas source Quality certified Yearly maintenance		Check for the connection to gas source Quality certified Yearly maintenance
Flowmeter	Flowmeters: • two columns (air and oxygen), • blender	Pressure check along the flow line Yearly system maintenance FiO ₂ formula $FiO_2 = \frac{(\text{air liter} \times 21) + (\text{oxygen liter} \times 100)}{\text{air liter} + \text{oxygen liter}}$	Flowmeters: • single O ₂ column flowmeter, • blender	Pressure check along the flow line Yearly system maintenance
Ventilator with humidifier	Heated breathing tube	Care of circuits and temperature sensor and heating cable of the circuits Circuits need Flow sensor maintenance and sterilization	-	-
Humidifier with integrated flow generator	Heated breathing tube	Circuits and filters need	-	-
Humidifier coupled with flowmeter or ventilator	-	Humidification circuit Temperature sensors Check of the system Yearly maintenance	-	-
Interfaces				
Nasal cannulas O ₂ standard	Evaluate: • fixing method (knowing how to correctly size and apply the cannula for the first time, understanding how to check that the cannula is fitted correctly, knowing how to remove and reapply the cannula when required); • cleaning and hygiene; • skin lesions (comfort to the septum and nares). Think over: • best interface; • right size; • patient's features; • flow you require; • other instruments (hood needs oximeter).			
Facial mask				
Hood				
Facial mask with reservoir "partial rebreathing"				
Facial mask with reservoir "non rebreathing"				
Nasal cannulas				
Venturi mask				
Monitoring devices				
Multiparametric system	x	Yearly system maintenance Supply check and maintenance of blood pressure cuff, sensors for SatO ₂ , ETCO ₂		Yearly system maintenance Supply check and maintenance of blood pressure cuff, sensors for SatO ₂ , ETCO ₂
Transcutaneous ETCO ₂	x	Yearly system maintenance Supply of disposable sensors		Yearly system maintenance Supply of disposable sensors
Saturimeter	x	Yearly system maintenance Supply of disposable sensors Supply of connection cables	x	Yearly system maintenance Supply of disposable sensors Supply of connection cables
Oximeter	x	Yearly system maintenance	x	Yearly system maintenance
Blood gas analysis	x	Yearly system maintenance Supply of materials	x	Yearly system maintenance Supply of materials

ETCO₂: end-tidal CO₂.

LECT 50

**MULTIDISCIPLINARY ROUND TABLE
WAITING TIMES: THE NURSE IN FRONT OF
END-OF-LIFE CHOICES (LECTURE I)**

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Although palliative care is quite recent in the field of neonatology, several clinical experiences have been published to date. [1-3]. The clinical uncertainty combined with the risk of dying are present in the units of neonatal intensive care. Professionals are confronted with very complex situations where emotional and ethical aspects are major and request a specific interdisciplinary approach. Models of pediatric palliative care in neonatology focus on several characteristics: the aim is to provide family-centered care [4], in which all family emotions are acknowledged and their needs addressed, comprehensive and integrative care, in which antenatal and postnatal care is included. Systematic individualized bereavement care can represent such postnatal care. According to the British Association of Perinatal Medicine, Perinatal palliative care is defined “as the planning and provision of supportive care during life and end-of-life care for a fetus, newborn infant or infant and their family in the management of an appropriate candidate condition. Candidate conditions for perinatal palliative care can be considered in five broad categories. Category 1: an antenatal or postnatal diagnosis of a condition, which is not compatible with long-term survival, e.g. bilateral renal agenesis or anencephaly. Category 2: an antenatal or postnatal diagnosis of a condition which carries a high risk of significant morbidity or death, e.g. severe bilateral hydronephrosis and impaired renal function. Category 3: babies born at the margins of viability, where intensive care has been deemed inappropriate. Category 4: postnatal clinical conditions with a high risk of severe impairment of quality of life and when the baby is receiving life support or may at some point require life support, e.g. severe hypoxic ischemic encephalopathy. Category 5: postnatal conditions which result in the baby experiencing “unbearable suffering” in the course of their illness or treatment, e.g. severe necrotizing enterocolitis, where palliative care is in the baby’s best interests [5]. Jay Milstein proposes

a change of paradigm where accompaniment is preponderant during the whole journey, whatever the prognosis is. She compares 3 models. The first one “series model of care” (a), once curative care has become futile, palliative care is initiated. In the second one called “parallel model of care” (b) curative measures progressively decreases and palliative measures are introduced simultaneously. In the so-called “integrative model of care” (c), healing and palliation are introduced in parallel with curative measures. As she writes: “Since a loss can be experienced even in the absence of death, bereavement is represented as a continual process from the outset. It usually undergoes an increase after death. In this paradigm, healing and bereavement are facilitated with a mindset of “being with” while curing is facilitated with the usual mindset of “doing to” [6]. Some terms such as “lethal malformations” or “incompatible with life” are not any more convenient, because some neonates with life-limiting diseases (e.g. Hypoplasia left ventricle or trisomy 18) actually survive and will have a higher expectancy of life than in the past [7]. The possibility to decide as parents to continuing a pregnancy, despite a life limiting disease were diagnosed requires a specific education of teams who accompany these families [8]. Recommendations and guidelines can help teams on this tough journey [9, 10].

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LECT 51

MULTIDISCIPLINARY ROUND TABLE WAITING TIMES: THE NURSE IN FRONT OF END-OF-LIFE CHOICES (LECTURE II)

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The nurse, as the deontological code of this profession (2009) reminds us, has the responsibility of assisting, treating and taking care of the person, out of respect for the life, health, liberty and dignity of the individual (art. 3). All of this requires special attention and application when treating a minor, keeping in mind their fragility/vulnerability and their age and level of maturity. To confront end of life decisions, a call back to some ethical values and principles like the following is important.

- a. *The centrality of the person and the recognition of his dignity*, in any situation and condition he may be in. The concept of dignity, in fact, entails not only the recognition of the preciousness of the person, but also the normative principle dictating the treatment of all human beings, from conception to death, in the respect of their value. In the realm of assisting the newborn with a fatal prognosis, it is a strong call to the nurse not to favor any other value over the patient and to never be absent, accompanying them in every phase of assistance.
- b. *The integral good of the person*, considering the physical dimension together with the psychological, spiritual and relational ones. Acting in the interest of the patient is the most ancient and universal principle recognized in the ethics of treatment. A biomedical good is certainly to be considered, which includes all of the effects of the clinical interventions on the natural progress of the sickness, but one cannot equate the whole good of the patient with the sole biomedical good: one must adopt a holistic

approach to capture all of the dimensions of the totality of the person.

- c. *The value and the protection of the human life up until its natural end*. Physical life is not exhausted in the meaning and the richness of the human person, however it represents its fundamental value insofar as it is co-essential for the realization of all the other values such as liberty, sociability, etc. which in the body and through the body are constructed and expressed. It is then the first duty and first right of each individual not only to respect but also to defend and the promote human life, independent of its phase of development, of health conditions, etc. Never, then, it is possible to think of a direct and deliberate suppression of the life of someone to favor the lives or better political-social conditions of others. We must realize these criteria especially in assistance in the context of the end of life. The value of human life, in fact, remains great also when health fails: one consideration is in fact the “being” of the human, another is his functionality. Life conserves its value also without perfect health.
- d. *Liberty and responsibility of the sick person*. If generally such a principle finds its application in the context of the relationship with a patient who is able to understand and have a will, in the neonatal area this calls to the importance of relationships and of the familial context; starting with the appropriate information given to parents about the situation of the neonate, and of the right of the parents to obtain complete, comprehensible and correct information. It is fundamentally important to establish good, constant and empathetic communications, so as to involve relatives adequately in the important decisions about treatment. The nurse – in a special way – participates in the decisions of the clinical team, involving the parents and, as far as possible, the minor, accompanying them in the end of life phase with palliative care and comfort.
- e. *The importance of “treating” and “assisting”* in the effort of conjugating these fundamental ethical experiences adequately. This principle finds special resonance in the context of accompaniment of the dying person, shedding light on the specific value of “taking care of,” on which the nursing profession is based.
- f. *Relieving pain and suffering*, remembering that suffering is a complex reality and that it involves the psychological and existential sphere.

g. *The proportionality of the treatments*, to avoid forms of aggressive medical treatment or euthanasia; the concept of therapeutic proportionality is fundamental in the medical practice. A treatment is ethically acceptable only if the foreseeable benefits are superior (or at least on a par) with the foreseeable risks. That means that one must intervene with the sick person in the measure in which it serves their health, no more and no less. If treated in the opposite way, the risk of falling into aggressive medical treatment, into pure experimentalism, into therapeutic abandonment becomes real. One should not, therefore, “medicalize” where it is not necessary, simply for interests foreign to health itself, nor should the necessary treatments be lacking, even if they are costly. It must be pointed out, then, that if the continual technological development of neonatology, supported by scientific research, has on the one hand allowed for the survival of

neonates born extremely prematurely or with complex pathologies, on the other hand it may also expose the little patients to therapeutic interventions that go beyond their capacities and possibilities of life only delaying the death event. These situations could be configured as aggressive medical treatment. The therapeutic insistence, in fact, in some situations cannot be in the best interests of the little patients with clinical conditions that can lead to the supposition of an unfavorable outcome. The risk of aggressive medical treatment weighs on neonatology doctors and nurses, representing a source of notable health unease.

h. *Reference to the values of justice and solidarity should never be lacking*, just as the relationship among hopes (with the lower-case “h”) must be kept intact and Hope, that is the hope that is still glimpsed when one has reached the point of being unable to be cured.